FORM PTO-1390 (REV. 12-2001) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER: 5/1269PCT

US APPLICATION NO. (If known, see 37 CFR 1.5): TO BE ASSIGNED 10/049795

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/EP00/07976	16 AUGUST 2000	20 AUGUST 1999

TITLE OF INVENTION
Substituted Piperazine Derivatives, the Preparation thereof and Their Use as Medicaments

APPLICANT(S) FOR DO/EO/US
Lehmann- Lintz, Thorsten; Heckel, Armin; Thomas, Leo; and Mark, Michael,

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☑ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☑ This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include items (5), (6), (9) and (21) indicated below.
4. ☑ The US has been elected by the expiration of 19 months from the priority date (Article 31).
5. ☑ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. ☐ is attached hereto (required only if not communicated by the International Bureau).
   b. ☑ has been communicated by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☑ An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).
   a. ☑ is attached hereto.
   b. ☐ has been previously submitted under 35 U.S.C. 154(d)(4).
7. ☑ Amendments to the claims of the International Aplication under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. ☐ are attached hereto (required only if not communicated by the International Bureau).
   b. ☐ have been communicated by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☑ have not been made and will not be made.
8. ☐ An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371 (c)(3)).
9. ☐ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. ☐ An English lanugage translation of the annexes of the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11 to 20 below concern document(s) or information included:

11. ☑ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. ☑ A FIRST preliminary amendment.
14. ☐ A SECOND or SUBSEQUENT preliminary amendment.
15. ☐ A substitute specification.
16. ☐ A change of power of attorney and/or address letter.
17. ☐ A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821 - 1.825.
18. ☐ A second copy of the published international application under 35 U.S.C. 154(d)(4).
19. ☐ A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).
20. ☑ Other items or information:
    Certified Copy of Priority document 199 39 516.0

U.S. APPLICATION NO (if known, see 37 CFR 1.5)	INTERNATIONAL APPLICATION NO	ATTORNEY'S DOCKET NUMBER
10/049795 TO BE ASSIGNED	PCT/EP00/07976	5/1269PCT

21 ☑ The following fees are submitted:

	CALCULATIONS PTO USE ONLY	
BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)):		
Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO **$1040.00**		
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO **$890.00**		
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO **$740.00**		
International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4) **$710.00**		
International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4) **$100.00**		
ENTER APPROPRIATE BASIC FEE AMOUNT =	$ 890.00	
Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☑ 30 months from the earliest claimed priority date (37 CFR 1.492(e)).	$ 130.00	

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total claims	9 - 20 =	0	x **$18.00**	$ 00	
Independent claims	2 - 3 =	0	x **$84.00**	$ 00	
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ **$280.00**	$	

TOTAL OF ABOVE CALCULATIONS =	$	
☐ Applicant claims small entity status. See 37 CFR 1.27. The fees indicated above are reduced by 1/2. +	$	
SUBTOTAL =	$	
Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☑ 30 months from the earliest claimed priority date (37 CFR 1.492(f)).	$ 130.00	
TOTAL NATIONAL FEE =	$ 1150.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00** per property +	$	
TOTAL FEES ENCLOSED =	$ 1150.00	
	Amount to be refunded:	$
	charged:	$

a. ☐ A check in the amount of $ _____ to cover the above fees is enclosed.

b. ☑ Please charge my Deposit Account No. 02-2955 in the amount of $ 1150.00 to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☑ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 02-2955 . A duplicate copy of this sheet is enclosed.

d. ☐ Fees are to be charged to a credit card. **WARNING:** Information on this form may become public. **Credit card information should not be included on this form.** Provide credit card information and authorization on PTO-2038.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137 (a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:
Robert P. Raymond
Boehringer Ingelheim Corporation
900 Ridgebury Road, P. O. Box 368
Ridgefield, CT 06877-0368
Date Mailed: February 13, 2002
Express Mail Airbill No. EL792016808

SIGNATURE

Anthony P. Bottino
NAME

41,629
REGISTRATION NUMBER

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of:	Lehmann-Lintz, T. et al	)Art Unit:	To be assigned
Serial No.:	To be Assigned	)Examiner:	To be assigned
Filed:	February 13, 2002		
Docket No.:	5/1269PCT		
Title:	Substituted Piperazine Derivatives, The Preparation Thereof and Their Use as Medicaments		

Box Patent Application
Commissioner For Patents
Washington, D.C. 20231

Sir:

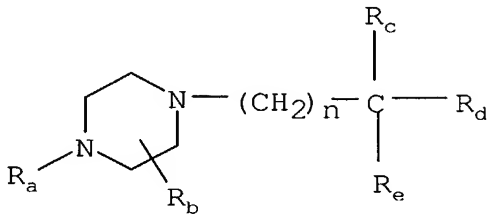
Please enter the following amendments and consider the following remarks before commencing examination of the above-captioned patent application.

In the claims:

Cancel claims 1-9

Please add the following new claims:

--10 (New). A compound the formula (I)



(I),

wherein

n denotes the number 3, 4 or 5,

R_a denotes a phenyl group substituted by the groups R_1 and R_2, wherein

R_1 denotes a hydrogen, fluorine, chlorine or bromine atom, a C_{1-3}-alkyl group wherein the hydrogen atoms are optionally wholly or partially replaced by fluorine atoms, a hydroxy, C_{1-4}-alkoxy, phenyl-C_{1-3}-alkoxy, carboxy, C_{1-3}-alkoxycarbonyl, aminocarbonyl, C_{1-3}-alkylaminocarbonyl, N,N-di-(C_{1-3}-alkyl)-aminocarbonyl, nitro, amino, C_{1-3}-alkylamino, di-(C_{1-3}-alkyl)-amino, phenyl-C_{1-3}-alkyl-amino, N-(C_{1-3}-alkyl)-phenyl-C_{1-3}-alkylamino, C_{1-3}-alkyl-carbonylamino, N-(C_{1-3}-alkyl)-C_{1-3}-alkylcarbonylamino, C_{1-3}-alkylsulphonylamino or N-(C_{1-3}-alkyl)-C_{1-3}-alkyl-sulphonylamino group and

R_2 denotes a hydrogen, fluorine, chlorine or bromine atom, a C_{1-3}-alkyl group or

R_1 and R_2 together denote a methylenedioxy group, a heteroaryl group, a monocyclic heteroaryl or phenyl group each of which is substituted by a phenyl or monocyclic heteroaryl group, while the abovementioned phenyl moieties are each optionally substituted by a fluorine, chlorine or bromine atom and the abovementioned phenyl moieties and heteroaryl groups are each optionally substituted by a C_{1-3}-alkyl group wherein the hydrogen atoms are optionally wholly or partially replaced by fluorine atoms, by a hydroxy, C_{1-3}-alkoxy, carboxy, C_{1-3}-alkoxycarbonyl, aminocarbonyl, C_{1-3}-alkylaminocarbonyl or N,N-di-(C_{1-3}-alkyl)-aminocarbonyl group,

R_b denotes a hydrogen atom or a C_{1-3}-alkyl group,

R_c denotes a hydrogen atom,
a C_{1-10}-alkyl, C_{3-7}-cycloalkyl or C_{3-7}-cycloalkyl-C_{1-3}-alkyl group wherein the hydrogen atoms in each case is optionally wholly or partially replaced by fluorine atoms,

a phenyl, naphthyl or heteroaryl group optionally substituted by a fluorine, chlorine or bromine atoms, by a C_{1-3}-alkyl group wherein the hydrogen atoms is optionally wholly or partially replaced by fluorine atoms, by a hydroxy, C_{1-3}-alkoxy, carboxy, C_{1-3}-alkoxycarbonyl, aminocarbonyl, C_{1-3}-alkylaminocarbonyl or N,N-di-(C_{1-3}-alkyl)-aminocarbonyl group, by a 3- to 7-membered cycloalkyleneimino group, while the

methylene group in position 4 of a 6- or 7-membered cycloalkyleneimino group may additionally be replaced by an oxygen or sulphur atom, by a sulphinyl, sulphonyl, imino or N-(C_{1-3}-alkyl)-imino group, by a nitro, amino, C_{1-3}-alkylamino, di-(C_{1-3}-alkyl)-amino, C_{1-3}-alkylcarbonylamino, N-(C_{1-3}-alkyl)-C_{1-3}-alkylcarbonylamino, C_{1-3}-alkylsulphonylamino or N-(C_{1-3}-alkyl)-C_{1-3}-alkylsulphonylamino group,

R_d denotes a phenyl, naphthyl or heteroaryl group each optionally substituted by a fluorine, chlorine or bromine atom, by a C_{1-3}-alkyl group wherein the hydrogen atoms are optionally wholly or partially replaced by fluorine atoms, by a hydroxy, C_{1-3}-alkoxy, carboxy, C_{1-3}-alkoxycarbonyl, aminocarbonyl, C_{1-3}-alkylaminocarbonyl or N,N-di-(C_{1-3}-alkyl)-aminocarbonyl group, by a 3- to 7-membered cycloalkyleneimino group, while the methylene group in the 4 position of a 6- or 7-membered cycloalkyleneimino group may additionally be replaced by an oxygen or sulphur atom, by a sulphinyl, sulphonyl, imino or N-(C_{1-3}-alkyl)-imino group, by a nitro, amino, C_{1-3}-alkylamino, di-(C_{1-3}-alkyl)-amino, C_{1-3}-alkylcarbonylamino, N-(C_{1-3}-alkyl)-C_{1-3}-alkylcarbonylamino, C_{1-3}-alkylsulphonylamino or N-(C_{1-3}-alkyl)-C_{1-3}-alkylsulphonylamino group, and

R_e denotes a carboxy group, a C_{1-6}-alkoxycarbonyl or C_{3-7}-cycloalkoxycarbonyl group, wherein the carbon atom of the alkoxycarbonyl group linked to the oxygen atom is a primary or secondary carbon atom and wherein the alkyl or cycloalkyl moiety of both groups are optionally substituted from position 2 in relation to the oxygen atom by a C_{1-3}-alkoxy, amino, C_{1-3}-alkylamino or di-(C_{1-3}-alkyl)-amino group, a phenyl-C_{1-3}-alkoxycarbonyl or heteroaryl-C_{1-3}-alkoxycarbonyl group,

while the abovementioned heteroaryl groups in this claim are
6-membered heteroaryl groups containing one, two or three nitrogen atoms,
and 5-membered heteroaryl groups, containing an imino group optionally substituted by a C_{1-3}-alkyl group, an oxygen or sulphur atom or an imino group optionally substituted by a C_{1-3}-alkyl group and an oxygen or sulphur atom or one or two nitrogen atoms,

or the isomers and the physiologically acceptable salts thereof.

11 (New). The compound the formula (I) according to claim 10, wherein

n denotes the number 3, 4 or 5,

R_a denotes a phenyl group which is substituted by the groups R_1 and R_2, wherein

R_1 denotes a hydrogen, chlorine or bromine atom, a C_{1-3}-alkyl, C_{1-3}-alkoxy, benzyloxy, carboxy, C_{1-3}-alkyloxycarbonyl, nitro, amino, acetamino or methanesulphonylamino group and

R_2 denotes a hydrogen, chlorine or bromine atom or a methyl group or

R_1 and R_2 together denote a methylenedioxy group,
a biphenyl group which is optionally substituted by a fluorine, chlorine or bromine atom, by a methyl, methoxy or trifluoromethyl group,
a pyridyl, pyrimidyl, pyrazinyl, pyridazinyl or thienyl group optionally substituted by a phenyl group or
a phenyl group substituted by a thienyl, thiazolyl, pyrrolyl, imidazolyl, pyridyl group or benzimidazolyl group,

R_b denotes a hydrogen atom,

R_c denotes a C_{1-3}-alkyl or phenyl group and

R_d denotes a phenyl group optionally substituted by a fluorine or chlorine atom or a methyl or methoxy group.

12 (New). The compound the formula (I) according to claim 11, wherein

n denotes the number 3 or 4,

R_a denotes a phenyl group which is substituted by the groups R_1 and R_2, wherein

R_1 denotes a hydrogen, chlorine or bromine atom, a C_{1-3}-alkyl, C_{1-3}-alkoxy or benzyloxy group and

R_2 denotes a hydrogen, chlorine or bromine atom or a methyl group,

R_1 and R_2 together denote a
a biphenyl group which is optionally substituted by a fluorine, chlorine or bromine atom, by a methyl, methoxy or trifluoromethyl group,

a pyridyl, pyrimidyl, pyrazinyl, pyridazinyl or thienyl group optionally substituted by a phenyl group or

a phenyl group substituted by a thienyl, thiazolyl, pyrrolyl, imidazolyl, pyridyl or benzimidazolyl group,

R_c denotes a C_{1-3}-alkyl group and

R_d denotes a phenyl group optionally substituted by a fluorine atom.

13 (New). A compound chosen from:

(a) methyl 2-ethyl-2-phenyl-5-[4-(4-chloro-phenyl)-piperazin-1-yl]-pentanoate,

(b) methyl 5-(4-biphenyl-4-yl-piperazin-1-yl)-2-ethyl-2-phenyl-pentanoate and

(c) methyl 5-(4-biphenyl-3-yl-piperazin-1-yl)-2-ethyl-2-phenyl-pentanoate

or the isomers and the physiologically acceptable salts thereof.

14 (New). A pharmaceutical composition comprising a pharmaceutically effective amount of a compound according to claim 10 and one or more pharmaceutically acceptable carriers and/or diluents.

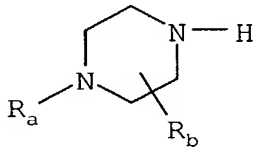
15 (New). A method of lowering plasma levels of atherogenic lipoproteins comprising administering to a patient in need thereof a pharmaceutically effective amount of a compound according to claim 10.

16(New). A method of treating hyperlipidaemias comprising administering to a patient in need thereof a pharmaceutically effective amount of a compound according to claim 10.

17(New). A method of treating or preventing a disorder chosen from atherosclerosis, diabetes mellitus, adiposity and pancreatitis comprising administering to a patient in need thereof a pharmaceutically effective amount of a compound according to claim 10.

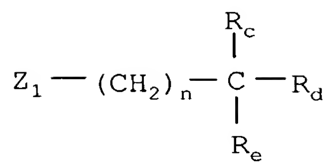
18 (New). A process for preparing a compound according to claims 10, said process comprising:

a) reacting under suitable conditions a compound of the formula (II):



(II)

wherein R_a and R_b are defined as in claim 10, with a compound of the formula (III)

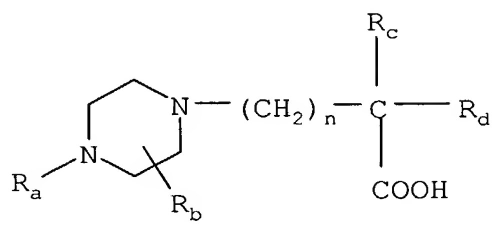


(III)

wherein n and R_c to R_e are defined as in claim 1 and Z_1 denotes a nucleofugic leaving group;

or

b) reacting by esterification under suitable conditions a compound of formula (IV):



(IV)

wherein

n and R_a to R_d are as defined in claim 10, or the reactive derivatives thereof, with an alcohol of the formula (V):

$$H - R_e' \quad (V),$$

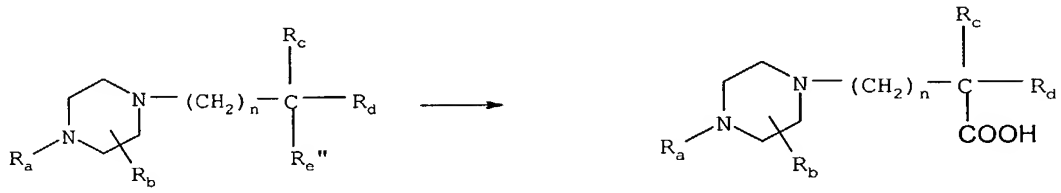
wherein

R_e' denotes a C_{1-6}-alkoxy or C_{3-7}-cycloalkoxy group wherein the alkyl or cycloalkyl moiety may in each case be substituted from the 2 position, relative to the oxygen atom, by a C_{1-3}-alkoxy, amino, C_{1-3}-alkylamino or di-(C_{1-3}-alkyl)-amino group, a phenyl-C_{1-3}-alkoxy or heteroaryl-C_{1-3}-alkoxy group, while the heteroaryl moiety is as hereinbefore defined, or

a tert.butyl ester is prepared by reacting with 2,2-dimethyl-ethene in the presence of an acid,

or

c) converting under suitable conditions a compound of the formula (VI) into a compound of the formula (I) in which R_e is defined as a carboxy group:



(VI) (I)

wherein

n and R_a to R_d are as defined in claim 10 and

R_e" denotes a group which can be converted into a carboxy group; and

for each of the above steps a-c, optionally subsequently:

reducing under suitable reducing conditions a compound of the formula (I) thus obtained which contains a nitro group into a corresponding amino compound and/or

deprotecting under suitable conditions any protecting groups used during the reactions; and

isolating compounds of the formula I thus obtained by resolving into its stereoisomers and/or converting into the physiologically acceptable salts thereof.---

Remarks

Claims 1-9 have been canceled. Claims 10 – 18 are now pending. Canceled claims 1-9 have been rewritten as new claims 10 –18 to be in accordance with US practice. No new matter has been added by way of amendment.

Respectfully submitted,

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"EXPRESS MAIL" LABEL NO.: EL792016808
DEPOSIT DATE: February 13, 2002

I HEREBY CERTIFY THAT THIS PAPER OR FEE IS BEING DEPOSITED WITH THE UNITED STATES POSTAL SERVICE "EXPRESS MAIL POST OFFICE TO ADDRESSEE" SERVICE UNDER 37 CFR 1.10 ON THE DATE INDICATED ABOVE AND IS ADDRESSED TO: BOX PATENT APPLICATION, THE COMMISSIONER FOR PATENTS, WASHINGTON, DC 20231.

By: _____
Anthony Bottino
Reg. No. 41,629

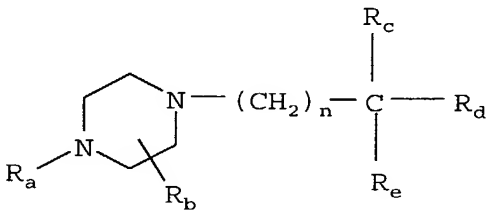
74403fft.205

Boehringer Ingelheim Pharma KG
D-55216 Ingelheim/Rhein

Case 5/1269-Fl
Foreign filing text

Substituted piperazine derivatives, the preparation thereof and their use as medicaments

The present invention relates to substituted piperazine derivatives of general formula



, (I)

their isomers, their salts, particularly the physiologically acceptable salts thereof which have valuable pharmacological properties.

The compounds of the above general formula I are valuable inhibitors of the microsomal triglyceride-transfer protein (MTP) and are therefore suitable for lowering the plasma level of the atherogenic lipoproteins.

In the above general formula I

n denotes the number 3, 4 or 5,

R_a denotes a phenyl group substituted by the groups R_1 and R_2, wherein

R_1 denotes a hydrogen, fluorine, chlorine or bromine atom, a C_{1-3}-alkyl group wherein the hydrogen atoms may be wholly or partially replaced by fluorine atoms, a hydroxy, C_{1-4}-alkoxy, phenyl-C_{1-3}-alkoxy, carboxy, C_{1-3}-alkoxycarbonyl, aminocarbonyl, C_{1-3}-alkylaminocarbonyl, N,N-di-(C_{1-3}-alkyl)-aminocarbonyl, nitro, amino, C_{1-3}-alkylamino, di-

(C_{1-3}-alkyl)-amino, phenyl-C_{1-3}-alkyl-amino, N-(C_{1-3}-alkyl)-phenyl-C_{1-3}-alkylamino, C_{1-3}-alkyl-carbonyl-amino, N-(C_{1-3}-alkyl)-C_{1-3}-alkylcarbonylamino, C_{1-3}-alkyl-sulphonylamino or N-(C_{1-3}-alkyl)-C_{1-3}-alkyl-sulphonylamino group and

R_2 denotes a hydrogen, fluorine, chlorine or bromine atom, a C_{1-3}-alkyl group or

R_1 and R_2 together denote a methylenedioxy group,

a heteroaryl group,

a monocyclic heteroaryl or phenyl group each of which is substituted by a phenyl or monocyclic heteroaryl group, while the abovementioned phenyl moieties may each be substituted by a fluorine, chlorine or bromine atom and the abovementioned phenyl moieties and heteroaryl groups may each be substituted by a C_{1-3}-alkyl group wherein the hydrogen atoms may be wholly or partially replaced by fluorine atoms, by a hydroxy, C_{1-3}-alkoxy, carboxy, C_{1-3}-alkoxycarbonyl, aminocarbonyl, C_{1-3}-alkylaminocarbonyl or N,N-di-(C_{1-3}-alkyl)-aminocarbonyl group,

R_b denotes a hydrogen atom or a C_{1-3}-alkyl group,

R_c denotes a hydrogen atom,

a C_{1-10}-alkyl, C_{3-7}-cycloalkyl or C_{3-7}-cycloalkyl-C_{1-3}-alkyl group wherein the hydrogen atoms in each case may be wholly or partially replaced by fluorine atoms,

a phenyl, naphthyl or heteroaryl group optionally substituted by a fluorine, chlorine or bromine atoms, by a C_{1-3}-alkyl group wherein the hydrogen atoms may be wholly or partially replaced by fluorine atoms, by a hydroxy, C_{1-3}-alkoxy, carboxy,

C_{1-3}-alkoxycarbonyl, aminocarbonyl, C_{1-3}-alkylaminocarbonyl or N,N-di-(C_{1-3}-alkyl)-aminocarbonyl group, by a 3- to 7-membered cycloalkyleneimino group, while the methylene group in position 4 of a 6- or 7-membered cycloalkyleneimino group may additionally be replaced by an oxygen or sulphur atom, by a sulphinyl, sulphonyl, imino or N-(C_{1-3}-alkyl)-imino group, by a nitro, amino, C_{1-3}-alkylamino, di-(C_{1-3}-alkyl)-amino, C_{1-3}-alkylcarbonylamino, N-(C_{1-3}-alkyl)-C_{1-3}-alkylcarbonylamino, C_{1-3}-alkylsulphonylamino or N-(C_{1-3}-alkyl)-C_{1-3}-alkylsulphonylamino group,

R_d denotes a phenyl, naphthyl or heteroaryl group optionally substituted by a fluorine, chlorine or bromine atom, by a C_{1-3}-alkyl group wherein the hydrogen atoms may be wholly or partially replaced by fluorine atoms, by a hydroxy, C_{1-3}-alkoxy, carboxy, C_{1-3}-alkoxycarbonyl, aminocarbonyl, C_{1-3}-alkylaminocarbonyl or N,N-di-(C_{1-3}-alkyl)-aminocarbonyl group, by a 3- to 7-membered cycloalkyleneimino group, while the methylene group in the 4 position of a 6- or 7-membered cycloalkyleneimino group may additionally be replaced by an oxygen or sulphur atom, by a sulphinyl, sulphonyl, imino or N-(C_{1-3}-alkyl)-imino group, by a nitro, amino, C_{1-3}-alkylamino, di-(C_{1-3}-alkyl)-amino, C_{1-3}-alkylcarbonylamino, N-(C_{1-3}-alkyl)-C_{1-3}-alkylcarbonylamino, C_{1-3}-alkylsulphonylamino or N-(C_{1-3}-alkyl)-C_{1-3}-alkylsulphonylamino group, and

R_e denotes a carboxy group, a C_{1-6}-alkoxycarbonyl or C_{3-7}-cycloalkoxycarbonyl group, wherein the carbon atom of the alkoxycarbonyl group linked to the oxygen atom is a primary or secondary carbon atom and wherein the alkyl or cycloalkyl moiety of both groups may be substituted from position 2 in relation to the oxygen atom by a C_{1-3}-alkoxy, amino, C_{1-3}-alkylamino or di-(C_{1-3}-alkyl)-amino group, a phenyl-C_{1-3}-alkoxycarbonyl or heteroaryl-C_{1-3}-alkoxycarbonyl group,

while the abovementioned heteroaryl groups are 6-membered heteroaryl groups containing one, two or three nitrogen atoms,

and 5-membered heteroaryl groups, containing an imino group optionally substituted by a C_{1-3}-alkyl group, an oxygen or sulphur atom, or an imino group optionally substituted by a C_{1-3}-alkyl group and an oxygen or sulphur atom or one or two nitrogen atoms.

Preferred compounds of the above general formula I are those wherein

R_e is as hereinbefore defined,

n denotes the number 3, 4 or 5,

R_a denotes a phenyl group which is substituted by the groups R_1 and R_2, while

R_1 denotes a hydrogen, chlorine or bromine atom, a C_{1-3}-alkyl, C_{1-3}-alkoxy, benzyloxy, carboxy, C_{1-3}-alkyloxycarbonyl, nitro, amino, acetamino or methanesulphonylamino group and

R_2 denotes a hydrogen, chlorine or bromine atom or a methyl group or

R_1 and R_2 together denote a methylenedioxy group,

a biphenyl group which may be substituted by a fluorine, chlorine or bromine atom, by a methyl, methoxy or trifluoromethyl group,

a pyridyl, pyrimidyl, pyrazinyl, pyridazinyl or thienyl group optionally substituted by a phenyl group or

a phenyl group substituted by a thienyl, thiazolyl, pyrrolyl, imidazolyl, pyridyl group or benzimidazolyl group,

R_b denotes a hydrogen atom,

R_c denotes a C_{1-3}-alkyl or phenyl group and

R_d denotes a phenyl group optionally substituted by a fluorine or chlorine atom or a methyl or methoxy group,

the isomers and the salts thereof.

Particularly preferred compounds of the above general formula I are those wherein

R_e is as hereinbefore defined,

n denotes the number 3 or 4,

R_a denotes a phenyl group which is substituted by the groups R_1 and R_2, wherein

R_1 denotes a hydrogen, chlorine or bromine atom, a C_{1-3}-alkyl, C_{1-3}-alkoxy or benzyloxy group and

R_2 denotes a hydrogen, chlorine or bromine atom or a methyl group,

a biphenyl group which may be substituted by a fluorine, chlorine or bromine atom, by a methyl, methoxy or trifluoromethyl group,

a pyridyl, pyrimidyl, pyrazinyl, pyridazinyl or thienyl group optionally substituted by a phenyl group or

a phenyl group substituted by a thienyl, thiazolyl, pyrrolyl, imidazolyl, pyridyl or benzimidazolyl group,

R_b denotes a hydrogen atom,

R_c denotes a C_{1-3}-alkyl group and

R_a denotes a phenyl group optionally substituted by a fluorine atom,

the isomers and the salts thereof.

The following are mentioned as examples of particularly valuable compounds:

(a) methyl 2-ethyl-2-phenyl-5-[4-(4-chlorophenyl)-piperazin-1-yl]-pentanoate,

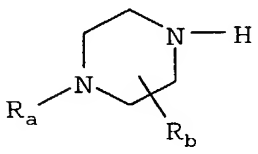
(b) methyl 5-(4-biphenyl-4-yl-piperazin-1-yl)-2-ethyl-2-phenyl-pentanoate and

(c) methyl 5-(4-biphenyl-3-yl-piperazin-1-yl)-2-ethyl-2-phenyl-pentanoate,

the isomers and the salts thereof.

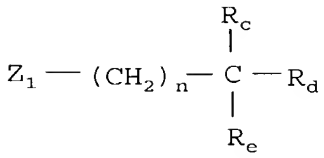
According to the invention, the new compounds are obtained by methods known from the literature, for example by the following methods:

a. reacting a compound of general formula



, (II)

wherein
R_a and R_b are as hereinbefore defined, with a compound of general formula



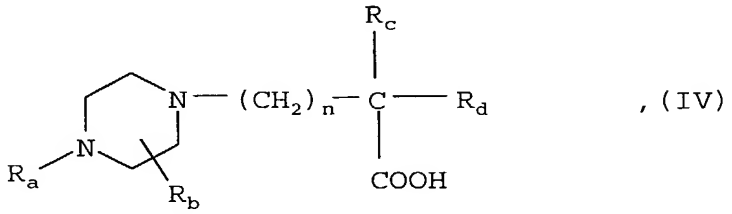
, (III)

wherein
n and R_c to R_e are as hereinbefore defined and
Z_1 denotes a nucleofugic leaving group such as a halogen atom, e.g. a chlorine, bromine or iodine atom.

The reaction is preferably carried out in a solvent such as methylene chloride, acetonitrile, tetrahydrofuran, toluene, acetone/water, dimethylformamide or dimethylsulphoxide optionally in the presence of a base such as sodium hydride, potassium carbonate, potassium tert-butoxide or N-ethyl-diisopropylamine at temperatures between 0 and 100°C, preferably at temperatures between 10 and 60°C.

b. In order to prepare a compound of general formula I, wherein R_e has the meanings given hereinbefore for R_e with the exception of the carboxy group:

esterifying a compound of general formula



, (IV)

wherein
n and R_a to R_d are as hereinbefore defined, or the reactive derivatives thereof with an alcohol of general formula

H - R_e' , (V)

wherein
R_e' denotes a C_{1-6}-alkoxy or C_{3-7}-cycloalkoxy group wherein the alkyl or cycloalkyl moiety may be substituted in each case from the 2 position, relative to the oxygen atom, by a C_{1-3}-alkoxy, amino, C_{1-3}-alkylamino or di-(C_{1-3}-alkyl)-amino group, a phenyl-C_{1-3}-alkoxy or heteroaryl-C_{1-3}-alkoxy group, while the heteroaryl moiety is as hereinbefore defined, or, in order to prepare a tert-butyl ester, 2,2-dimethyl-ethene, in the presence of an acid.

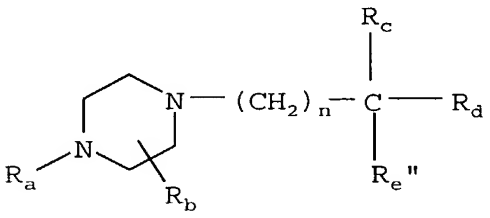
The reaction is optionally carried out in the presence of a solvent or mixture of solvents such as methylene chloride, dimethylformamide, benzene, toluene, chlorobenzene, tetrahydrofuran, benzene/tetrahydrofuran or dioxane, but preferably in an excess of the alcohol of general formula V used as solvent, optionally in the presence of an acid such as hydrochloric acid or sulphuric acid or in the presence of a dehydrating agent, e.g. in the presence of isobutyl chloroformate, tetraethyl orthocarbonate, trimethyl orthoacetate, 2,2-dimethoxypropane, tetramethoxysilane, thionyl chloride, trimethylchlorosilane, phosphorus trichloride, phosphorus pentoxide, N,N'-dicyclohexyl-carbodiimide, N,N'-dicyclohexylcarbodiimide/N-hydroxy-succinimide, N,N'-dicyclohexylcarbodiimide/1-hydroxy-benzotriazole, 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium-tetrafluoroborate, 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium-tetrafluoroborate/1-hydroxy-benzotriazole, N,N'-carbonyldiimidazole or triphenylphosphine/carbon tetrachloride, and optionally with the addition of a base such as pyridine, 4-dimethylaminopyridine, N-methyl-morpholine or triethylamine, appropriately at temperatures between 0 and 150°C, preferably at temperatures between 0 and 100°C.

The reaction of a corresponding reactive compound of general formula IV such as the esters, imidazolides or halides with an alcohol of general formula V is preferably carried out in a corresponding alcohol as solvent, optionally in the presence of another solvent such as methylene chloride or ether and preferably in the presence of a tertiary organic base such as triethylamine, N-ethyl-diisopropylamine or N-methyl-morpholine at temperatures between 0 and 150°C, preferably at temperatures between 50 and 100°C.

The formation of the tert.butyl ester with 2,2-dimethyl-ethene is preferably carried out in a solvent such as diethyl ether, dioxane, methylene chloride or tert.butanol in the presence of an acid such as sulphuric acid, hydrochloric acid or boron fluoride-diethyletherate at temperatures between -20 and 150°C, preferably at temperatures between 0 and 100°C.

c. In order to prepare a compound of general formula I wherein R_e denotes a carboxy group:

converting a compound of general formula



, (VI)

wherein
n and R_a to R_d are as hereinbefore defined and
R_e" denotes a group which can be converted into a carboxy group, into a compound of general formula I wherein R_e denotes a carboxy group.

The group which may be converted into a carboxy group may be, for example, a carboxyl group protected by a protecting group,

such as the functional derivatives thereof, e.g. the unsubstituted or substituted amides, esters, thioesters, trimethylsilyl esters, orthoesters or iminoesters thereof, which may expediently be converted by hydrolysis into a carboxyl group,

the esters thereof with tertiary alcohols, e.g. the tert. butyl ester, which are expediently converted into a carboxyl group by treating with an acid or thermolysis, and

the esters thereof with aralkanols, e.g. the benzyl ester, which are expediently converted into a carboxyl group by hydrogenolysis.

The hydrolysis is expediently carried out either in the presence of an acid such as hydrochloric acid, sulphuric acid, phosphoric acid, acetic acid, trichloroacetic acid, trifluoroacetic acid or mixtures thereof or in the presence of a base such as lithium hydroxide, sodium hydroxide or potassium hydroxide in a suitable solvent such as water, water/methanol, water/ethanol, water/isopropanol, methanol, ethanol, water/tetrahydrofuran or water/dioxane at temperatures between -10 and 120°C, e.g. at temperatures between ambient temperature and the boiling temperature of the reaction mixture.

If R_e" in a compound of formula VI denotes the tert. butyloxycarbonyl group, for example, this may also be cleaved by treating with an acid such as trifluoroacetic acid, formic acid, p-toluenesulphonic acid, sulphuric acid, hydrochloric acid, phosphoric acid or polyphosphoric acid optionally in an inert solvent such as methylene chloride, chloroform, benzene, toluene, diethyl ether, tetrahydrofuran or dioxane preferably at temperatures between -10 and 120°C, e.g. at temperatures between 0 and 60°C, or thermally, optionally in an inert solvent such as methylene chloride, chloroform, benzene, toluene, tetrahydrofuran or dioxane and preferably in the presence of a catalytic amount of an acid such as

p-toluenesulphonic acid, sulphuric acid, phosphoric acid or polyphosphoric acid preferably at the boiling temperature of the solvent used, e.g. at temperatures between 40 and 120°C.

If R_e" in a compound of formula VI denotes the benzyloxycarbonyl group, for example, this may also be cleaved hydrogenolytically in the presence of a hydrogenation catalyst such as palladium/charcoal in a suitable solvent such as methanol, ethanol, ethanol/water, glacial acetic acid, ethyl acetate, dioxane or dimethylformamide, preferably at temperatures between 0 and 50°C, e.g. at ambient temperature, and at a hydrogen pressure of 1 to 5 bar.

If according to the invention a compound of general formula I is obtained which contains a nitro group it may be converted by reduction into a corresponding amino compound.

The subsequent reduction of a nitro group is expediently carried out hydrogenolytically, e.g. with hydrogen in the presence of a catalyst such as platinum, palladium/charcoal or Raney nickel in a suitable solvent such as methanol, ethanol, ethyl acetate, tetrahydrofuran, dioxane, dimethylformamide or glacial acetic acid, optionally with the addition of an acid such as hydrochloric acid and at a hydrogen pressure of 1 to 7 bar, but preferably 1 to 5 bar, with metals such as iron, tin or zinc in the presence of an acid such as acetic acid or hydrochloric acid, with salts such as iron(II)sulphate, tin (II) chloride, sodium sulphide, sodium hydrogen sulphite or sodium dithionite, or with hydrazine in the presence of Raney nickel at temperatures between 0 and 100°C, but preferably at temperatures between 20 and 60°C.

In the reactions described hereinbefore, any reactive groups present such as hydroxy, carboxy, amino, alkylamino or imino groups may be protected during the reaction by conventional protecting groups which are cleaved again after the reaction.

For example, a protecting group for a hydroxy group may be a trimethylsilyl, tert.butyl-dimethylsilyl, acetyl, benzoyl, methyl, ethyl, tert.butyl, trityl, benzyl or tetrahydropyranyl group,

a protecting group for a carboxyl group may be a trimethylsilyl, methyl, ethyl, tert.butyl, benzyl or tetrahydropyranyl group and

protecting groups for an amino, alkylamino or imino group may be a formyl, acetyl, trifluoroacetyl, ethoxycarbonyl, tert.butoxycarbonyl, benzyloxycarbonyl, benzyl, methoxybenzyl or 2,4-dimethoxybenzyl group and additionally, for the amino group, a phthalyl group.

Any protecting group used is optionally subsequently cleaved for example by hydrolysis in an aqueous solvent, e.g. in water, isopropanol/water, acetic acid/water, tetrahydrofuran/water or dioxane/water, in the presence of an acid such as trifluoroacetic acid, hydrochloric acid or sulphuric acid or in the presence of an alkali metal base such as sodium hydroxide or potassium hydroxide or aprotically, e.g. in the presence of iodotrimethylsilane, at temperatures between 0 and 120°C, preferably at temperatures between 10 and 100°C. However, a silyl group may also be cleaved using tetrabutylammonium fluoride as described hereinbefore.

However, a benzyl, methoxybenzyl or benzyloxycarbonyl group is cleaved for example hydrogenolytically, e.g. with hydrogen in the presence of a catalyst such as palladium/charcoal in a suitable solvent such as methanol, ethanol, ethyl acetate or glacial acetic acid, optionally with the addition of an acid such as hydrochloric acid at temperatures between 0 and 100°C, but preferably at temperatures between 20 and 60°C, and at a hydrogen pressure of 1 to 7 bar, but preferably 3 to 5 bar. A 2,4-dimethoxybenzyl group, however, is preferably cleaved in trifluoroacetic acid in the presence of anisole.

A tert.butyl or tert.butyloxycarbonyl group is preferably cleaved by treating with an acid such as trifluoroacetic acid or hydrochloric acid or by treating with iodotrimethylsilane, optionally using a solvent such as methylene chloride, dioxane, methanol or diethyl ether.

A trifluoroacetyl group is preferably cleaved by treating with an acid such as hydrochloric acid, optionally in the presence of a solvent such as acetic acid at temperatures between 50 and 120°C or by treating with sodium hydroxide solution, optionally in the presence of a solvent such as tetrahydrofuran at temperatures between 0 and 50°C.

A phthalyl group is preferably cleaved in the presence of hydrazine or a primary amine such as methylamine, ethylamine or n-butylamine in a solvent such as methanol, ethanol, isopropanol, toluene/water or dioxane at temperatures between 20 and 50°C.

Moreover, the compounds of general formula I obtained may be resolved into their enantiomers and/or diastereomers, as mentioned hereinbefore. Thus, for example, cis/trans mixtures may be resolved into their cis and trans isomers, and compounds with at least one optically active carbon atom may be separated into their enantiomers.

Thus, for example, the cis/trans mixtures may be resolved by chromatography into the cis and trans isomers thereof, the compounds of general formula I obtained which occur as racemates may be separated by methods known *per se* (cf. Allinger N. L. and Eliel E. L. in "Topics in Stereochemistry", Vol. 6, Wiley Interscience, 1971) into their optical antipodes and compounds of general formula I with at least 2 asymmetric carbon atoms may be resolved into their diastereomers on the basis of their physical-chemical differences using methods known *per se*, e.g. by chromatography and/or fractional

crystallisation, and, if these compounds are obtained in racemic form, they may subsequently be resolved into the enantiomers as mentioned above.

The enantiomers are preferably separated by column separation on chiral phases or by recrystallisation from an optically active solvent or by reacting with an optically active substance which forms salts or derivatives such as e.g. esters or amides with the racemic compound, particularly acids and the activated derivatives or alcohols thereof, and separating the diastereomeric mixture of salts or derivatives thus obtained, e.g. on the basis of their differences in solubility, whilst the free antipodes may be released from the pure diastereomeric salts or derivatives by the action of suitable agents. Optically active acids in common use are e.g. the D- and L-forms of tartaric acid or dibenzoyltartaric acid, di-o-tolyltartaric acid, malic acid, mandelic acid, camphorsulphonic acid, glutamic acid, aspartic acid or quinic acid. An optically active alcohol may be for example (+) or (-)-menthol and an optically active acyl group in amides, for example, may be a (+)-or (-)-menthyloxycarbonyl.

Furthermore, the compounds of formula I may be converted into the salts thereof, particularly for pharmaceutical use into the physiologically acceptable salts with inorganic or organic acids. Acids which may be used for this purpose include for example hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, fumaric acid, succinic acid, lactic acid, citric acid, tartaric acid or maleic acid.

Moreover, if the new compounds of formula I thus obtained contain an acidic group such as a carboxy group, they may subsequently, if desired, be converted into the salts thereof with inorganic or organic bases, particularly for pharmaceutical use into the physiologically acceptable salts thereof. Suitable bases for this purpose include for example sodium hydroxide, potassium hydroxide, arginine,

cyclohexylamine, ethanolamine, diethanolamine and triethanolamine.

The compounds of general formulae II to VI used as starting materials are known from the literature in some cases or may be obtained by methods known from the literature or are described in the Examples. Thus, for example, a compound of general formula III is obtained by esterifying a corresponding disubstituted carboxylic acid and subsequently reacting with an α,ω-dihaloalkane in the presence of a strong base such as lithium diisopropylamide, sodium amide or sodium hydride.

As already mentioned hereinbefore, the compounds of general formula I and the physiologically acceptable salts thereof have valuable pharmacological properties. In particular, they are valuable inhibitors of the microsomal triglyceride-transfer protein (MTP) and are therefore suitable for lowering the plasma levels of the atherogenic lipoproteins.

For example, the compounds according to the invention were investigated for their biological effects as follows:

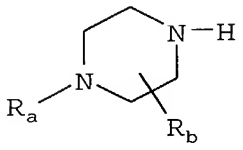
Inhibitors of MTP were identified by a commercially obtainable MTP activity kit (WAK-Chemie Medical GmbH, Sulzbacherstrasse 15-21, D-65812 Bad Soden, Germany). This test kit contains donor and acceptor particles. The donor particles contain fluorescence-labelled triglycerides in a concentration high enough to cause self-extinction of the fluorescence. When the donor and acceptor particles were incubated with an MTP source, fluorescence-labelled triglycerides were transferred from the donor to the acceptor particles. This led to an increase in the fluorescence in the sample. Solubilised liver microsomes from various species (e.g. rat) could be used as the MTP source. Inhibitors of MTP were identified as the substances which reduced the transfer of fluorescence-labelled triglycerides compared with a control mixture with no inhibitor.

In view of the abovementioned biological properties the compounds of general formula I and the physiologically acceptable salts thereof are particularly suitable for lowering the plasma concentration of atherogenic apolipoprotein B (apoB)-containing lipoproteins such as chylomicrons and/or very low density lipoproteins (VLDL) as well as the residues thereof such as low density lipoproteins (LDL) and/or lipoprotein(a) (Lp(a)), for treating hyperlipidaemias, for preventing and treating atherosclerosis and the clinical sequelae thereof, and for preventing and treating related disorders such as diabetes mellitus, adiposity and pancreatitis, oral administration being preferred.

The daily dose needed to achieve such an effect is between 0.5 and 500 mg, expediently between 1 and 350 mg, but preferably between 5 and 200 mg, in adults.

For this purpose, the compounds of formula I prepared according to the invention, optionally combined with other active substances such as other lipid-lowering agents, for example HMG-CoA-reductase inhibitors, cholesterol biosynthesis inhibitors such as squalene synthase inhibitors and squalene cyclase inhibitors, bile acid-binding resins, fibrates, cholesterol resorption inhibitors, niacin, probucol, CETP inhibitors and ACAT inhibitors may be incorporated together with one or more inert conventional carriers and/or diluents, e.g. with corn starch, lactose, glucose, microcrystalline cellulose, magnesium stearate, polyvinylpyrrolidone, citric acid, tartaric acid, water, water/ethanol, water/glycerol, water/sorbitol, water/polyethylene glycol, propylene glycol, cetylstearyl alcohol, carboxymethylcellulose or fatty substances such as hard fat or suitable mixtures thereof into conventional galenic preparations such as plain or coated tablets, capsules, powders, suspensions or suppositories.

The invention further relates to the intermediate products of general formula

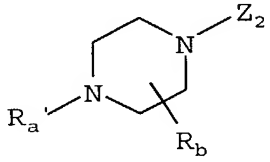


, (VII)

wherein

R_a and R_b are as hereinbefore defined, and the salts thereof.

The compounds of general formula VII are obtained by methods known from the literature, for example by reacting a compound of general formula



, (VIII)

wherein R_b is as hereinbefore defined, Z_2 denotes a protecting group for an amino group, for example the tert.butoxycarbonyl or benzyloxycarbonyl group, and R_a' denotes for example a phenyl or monocyclic heteroaryl group substituted by a bromine or iodine atom, with a monocyclic aryl or heteroaryl group substituted by trifluoromethyl, for example, which is additionally substituted by a boric acid group, in the presence of a catalyst such as for example palladium acetate, a base such as potassium tert.butoxide and a phase transfer catalyst such as tetrabutylammonium iodide in a solvent such as, for example, water, DMF, toluene or mixtures thereof at temperatures between 20 and 130°C. The protecting group is cleaved using methods known from the literature and leads to a compound of general formula VII.

The Examples that follow are intended to illustrate the invention:

Example 1

Methyl 2-methyl-2-phenyl-5-(4-phenyl-piperazin-1-yl)-pentanoate

a. Methyl 2-phenylpropionate

50 g (0.3 mol) of 2-phenylpropionic acid are dissolved in 375 ml of methanolic hydrochloric acid and stirred for 14 hours at ambient temperature. The solvent is removed and the residue is extracted with ethyl acetate and saturated sodium hydrogen carbonate solution. The organic phases are extracted with water and saturated saline solution, dried over magnesium sulphate and evaporated down.
Yield: 51 g (94.8% of theory).

b. Methyl 5-bromo-2-methyl-2-phenyl-pentanoate

15 g of n-butyllithium (0.234 mol) as a 2.5-molar solution in hexane are added dropwise at -30°C to a solution of 32.8 ml (0.234 mol) of diisopropylamine in 200 ml of anhydrous tetrahydrofuran and the mixture is stirred for ten minutes at -10°C. At -76°C 38.4 g (0.234 mol) of methyl 2-phenylpropionate are added dropwise and the mixture is stirred for 30 minutes at this temperature. Then 26.3 ml (0.257 mol) of 1,3-dibromopropane are added, after the addition has ended the cooling bath is removed and the mixture is stirred for 14 hours at ambient temperature. The reaction solution is poured onto 1.2 l of water and extracted with diethylether. The organic phases are extracted with water, dried over sodium sulphate and the solvent is eliminated. The residue is distilled under a high vacuum.
Yield: 42.7 g (64 % of theory),
Boiling point: 113-118°C at 0.2 mbar.

c. Methyl 2-methyl-2-phenyl-5-(4-phenyl-piperazin-1-yl)-pentanoate

A solution of 1 g (0.006 mol) of 1-phenylpiperazine, 1.71 g (0.006 mol) of methyl 5-bromo-2-methyl-2-phenyl-pentane carboxylate and 0.836 ml (0.006 mol) of triethylamine in 40 ml of methanol is stirred for 42 hours at ambient temperature. The reaction solution is evaporated down, combined with saturated sodium hydrogen carbonate solution and extracted with ethyl acetate. The organic phase is dried over sodium sulphate. Purification is carried out by column chromatography on silica gel (eluant: dichloromethane/ethanol = 40:1).
Yield: 0.66 g (29.2 % of theory),
$C_{23}H_{30}N_2O_2$ (M = 366.50)

Calculated: molecular peak $(M)^+$ = 366

Found: molecular peak $(M)^+$ = 366

Example 2

Methyl 2-methyl-2-phenyl-5-(4-pyridin-2-yl-piperazin-1-yl)-pentanoate

A suspension of 0.185 g (0.001 mol) of 1-pyridin-2-yl-piperazine, 0.324 g (0.001 mol) of methyl 5-bromo-2-methyl-2-phenyl-pentanoate, 0.1 ml of water and 0.2 g (0.001 mol) of potassiuim carbonate in 20 ml of acetonitrile is stirred for 6 hours at 60°C. Then the reaction solution is mixed with water and extracted with ethyl acetate. The organic phase is dried over sodium sulphate. Purification is carried out by column chromatography on silica gel (eluant: dichloromethane/ethanol = 20:1).
Yield: 0.21 g (52.3 % of theory),
$C_{22}H_{29}N_3O_2$ (M = 367.49)

Calc.: molecular peak $(M)^+$ = 367

Found: molecular peak $(M)^+$ = 367

Example 3

Methyl 2-methyl-2-phenyl-5-(4-pyrazin-2-yl-piperazin-1-yl)-pentanoate

Prepared analogously to Example 2 from 1-pyrazin-2-yl-piperazine and methyl 5-bromo-2-methyl-2-phenyl-pentanoate.
Yield: 0.1 g (23.9 % of theory),
$C_{21}H_{28}N_4O_2$ (M = 368.48)

Calc.: molecular peak $(M)^+$ = 368

Found: molecular peak $(M)^+$ = 368

Example 4

Methyl 2-methyl-2-phenyl-5-[4-(2-chloro-phenyl)-piperazin-1-yl]-pentanoate

Prepared analogously to Example 2 from 1-(2-chloro-phenyl)-piperazine and methyl 5-bromo-2-methyl-2-phenyl-pentanoate.
Yield: 0,2 g (28.4 % of theory),
$C_{23}H_{29}ClN_2O_2$ (M = 400,95)

Calc.: molecular peak $(M)^+$ = 400/402

Found: molecular peak $(M)^+$ = 400/402

Example 5

Methyl 2-methyl-2-phenyl-5-[4-(3-chloro-phenyl)-piperazin-1-yl]-pentanoate

Prepared analogously to Example 2 from 1-(3-chloro-phenyl)-piperazine and methyl 5-bromo-2-methyl-2-phenyl-pentanoate.
Yield: 0,24 g (34.1 % of theory),
$C_{23}H_{29}ClN_2O_2$ (M = 400.95)

Calc.: molecular peak $(M)^+$ = 400/402

Found: molecular peak $(M)^+$ = 400/402

Example 6

Methyl 2-methyl-2-phenyl-5-[4-(4-chloro-phenyl)-piperazin-1-yl]-pentanoate

Prepared analogously to Example 2 from 1-(4-chloro-phenyl)-piperazine and methyl 5-bromo-2-methyl-2-phenyl-pentanoate.
Yield: 0.2 g (28.4 % of theory),
$C_{23}H_{29}ClN_2O_2$ (M = 400.95)

Calc.: molecular peak $(M)^+$ = 400/402

Found: molecular peak $(M)^+$ = 400/402

Example 7

Methyl 2-methyl-2-phenyl-5-[4-(3,5-dichloro-phenyl)-piperazin-1-yl]-pentanoate

Prepared analogously to Example 2 from 1-(3,5-dichloro-phenyl)-piperazine and methyl 5-bromo-2-methyl-2-phenyl-pentanoate.
Yield: 0.25 g (26.2 % of theory),
$C_{23}H_{28}Cl_2N_2O_2$ (M = 435.39)

Calc.: molecular peak $(M)^+$ = 434/436/438

Found: molecular peak $(M)^+$ = 434/436/438

Example 8

Methyl 2-methyl-2-phenyl-5-[4-(2-bromo-phenyl)-piperazin-1-yl]-pentanoate

Prepared analogously to Example 2 from 1-(2-bromo-phenyl)-piperazine and methyl 5-bromo-2-methyl-2-phenyl-pentanoate.
Yield: 0.3 g (38.4 % of theory),
$C_{23}H_{29}BrN_2O_2$ (M = 445.40)

Calc.: molecular peak $(M)^+$ = 444/446

Found: molecular peak $(M)^+$ = 444/446

Example 9

Methyl 2-methyl-2-phenyl-5-[4-(4-bromo-phenyl)-piperazin-1-yl]-pentanoate

Prepared analogously to Example 2 from 1-(4-bromo-phenyl)-piperazine and methyl 5-bromo-2-methyl-2-phenyl-pentanoate.
Yield: 0.25 g (32 % of theory),
$C_{23}H_{29}BrN_2O_2$ (M = 445.40)

Calc.: molecular peak $(M)^+$ = 444/446

Found: molecular peak $(M)^+$ = 444/446

Example 10

Methyl 2-methyl-2-phenyl-5-[4-(2-methyl-phenyl)-piperazin-1-yl]-pentanoate

Prepared analogously to Example 2 from 1-(methyl-2-methyl-phenyl)-piperazine and methyl 5-bromo-2-methyl-2-phenyl-pentanoate.
Yield: 0.21 g (49.6 % of theory),
$C_{24}H_{32}N_2O_2$ (M = 380.53)

Calc.: molecular peak $(M)^+$ = 380

Found: molecular peak $(M)^+$ = 380

Example 11

Methyl 2-methyl-2-phenyl-5-[4-(3-methyl-phenyl)-piperazin-1-yl]-pentanoate

Prepared analogously to Example 2 from 1-(3-methyl-phenyl)-piperazine and methyl 5-bromo-2-methyl-2-phenyl-pentanoate.
Yield: 0.2 g (30 % of theory),
$C_{24}H_{32}N_2O_2$ (M = 380.53)

Calc.: molecular peak $(M)^+$ = 380

Found: molecular peak $(M)^+$ = 380

Example 12

Methyl 2-methyl-2-phenyl-5-[4-(4-methyl-phenyl)-piperazin-1-yl]-pentanoate

Prepared analogously to Example 2 from 1-(4-methyl-phenyl)-piperazine and methyl 5-bromo-2-methyl-2-phenyl-pentanoate.

Yield: 0.22 g (51.6 % of theory),
$C_{24}H_{32}N_2O_2$ (M = 380.53)

Calc.: molecular peak $(M)^+$ = 380

Found: molecular peak $(M)^+$ = 380

Example 13

Methyl 2-methyl-2-phenyl-5-[4-(3,4-dimethyl-phenyl)-piperazin-1-yl]-pentanoate

Prepared analogously to Example 2 from 1-(3,4-dimethyl-phenyl)-piperazine and methyl 5-bromo-2-methyl-2-phenyl-pentanoate.
Yield: 0.25 g (36.1 % of theory),
$C_{25}H_{34}N_2O_2$ (M = 394.56)

Calc.: molecular peak $(M)^+$ = 394

Found: molecular peak $(M)^+$ = 394

Example 14

Methyl 2-methyl-2-phenyl-5-[4-(4-ethyl-phenyl)-piperazin-1-yl]-pentanoate

Prepared analogously to Example 2 from 1-(4-ethyl-phenyl)-piperazine and methyl 5-bromo-2-methyl-2-phenyl-pentanoate.
Yield: 0.11 g (33.2 % of theory),
$C_{25}H_{34}N_2O_2$ (M = 394.56)

Calc.: molecular peak $(M)^+$ = 394

Found: molecular peak $(M)^+$ = 394

Example 15

Methyl 2-methyl-2-phenyl-5-[4-(2-methoxy-phenyl)-piperazin-1-yl]-pentanoate

Prepared analogously to Example 2 from 1-(2-methoxy-phenyl)-piperazine and methyl 5-bromo-2-methyl-2-phenyl-pentanoate.
Yield: 1.45 g (69.7 % of theory),

$C_{24}H_{32}N_2O_3$ (M = 396.53)

Calc.: molecular peak $(M)^+$ = 396

Found: molecular peak $(M)^+$ = 396

Example 16

Methyl 2-methyl-2-phenyl-5-[4-(3-methoxy-phenyl)-piperazin-1-yl]-pentanoate

Prepared analogously to Example 2 from 1-(3-methoxy-phenyl)-piperazine and methyl 5-bromo-2-methyl-2-phenyl-pentanoate.
Yield: 1.65 g (79.3 % of theory),
$C_{24}H_{32}N_2O_3$ (M = 396.53)

Calc.: molecular peak $(M)^+$ = 396

Found: molecular peak $(M)^+$ = 396

Example 17

Methyl 2-methyl-2-phenyl-5-[4-(4-methoxy-phenyl)-piperazin-1-yl]-pentanoate

Prepared analogously to Example 2 from 1-(4-methoxy-phenyl)-piperazine and methyl 5-bromo-2-methyl-2-phenyl-pentanoate.
Yield: 1.67 g (80.3 % of theory),
Melting point: 62-65°C
$C_{24}H_{32}N_2O_3$ (M = 396.53)

Calc.: molecular peak $(M)^+$ = 396

Found: molecular peak $(M)^+$ = 396

Example 18

Methyl 2-methyl-2-phenyl-5-[4-(2-ethoxy-phenyl)-piperazin-1-yl]-pentanoate

Prepared analogously to Example 2 from 1-(2-ethoxy-phenyl)-piperazine and methyl 5-bromo-2-methyl-2-phenyl-pentanoate.
Yield: 1.54 g (64.5 % of theory),
$C_{25}H_{34}N_2O_3$ (M = 410.56)

Calc.: molecular peak $(M)^+$ = 410

Found: molecular peak $(M)^+$ = 410

Example 19

Methyl 2-methyl-2-phenyl-5-[4-(4-benzyloxy-phenyl)-piperazin-1-yl]-pentanoate

Prepared analogously to Example 2 from 1-(4-benzyloxy-phenyl)-piperazine and methyl 5-bromo-2-methyl-2-phenyl-pentanoate.

Yield: 0.29 g (64.6 % of theory),

Melting point: 82-83°C

$C_{30}H_{36}N_2O_3$ (M = 472.63)

Calc.: molecular peak $(M)^+$ = 472

Found: molecular peak $(M)^+$ = 472

Example 20

Methyl 2-methyl-2-phenyl-5-[4-(benzo[1,3]dioxol-5-yl)-piperazin-1-yl]-pentanoate

Prepared analogously to Example 2 from 1-benzo[1,3]dioxol-5-yl-piperazine and methyl 5-bromo-2-methyl-2-phenyl-pentanoate.

Yield: 0.18 g (25 % of theory)

Example 21

Methyl 2-methyl-2-phenyl-5-[4-(4-nitro-phenyl)-piperazin-1-yl]-pentanoate

Prepared analogously to Example 2 from 1-(4-nitro-phenyl)-piperazine and methyl 5-bromo-2-methyl-2-phenyl-pentanoate.

Yield: 5.3 g (73.5 % of theory),

Melting point: 123-124°C

$C_{23}H_{29}N_3O_4$ (M = 411.50)

Calc.: molecular peak $(M)^+$ = 411

Found: molecular peak $(M)^+$ = 411

Example 22

Methyl 2-methyl-2-phenyl-5-[4-(4-amino-phenyl)-piperazin-1-yl]-pentanoate

A suspension of 5 g (0.012 mol) of methyl 2-methyl-2-phenyl-5-[4-(4-nitro-phenyl)-piperazin-1-yl]-pentanoate, 1 g of palladium (10% on charcoal) in 200 ml of ethyl acetate and 100 ml of methanol is stirred for four hours at ambient temperature in a Parr apparatus under 50 psi hydrogen pressure. The catalyst is filtered off and activated charcoal is added to the filtrate. After removal of the activated charcoal the solvent is distilled off.

Yield: 4.25 g (91.7 % of theory),

$C_{23}H_{31}N_3O_2$ (M = 381.52)

Calc.: molecular peak $(M)^+ = 381$

Found: molecular peak $(M)^+ = 381$

Example 23

Methyl 2-methyl-2-phenyl-5-[4-(4-acetylamino-phenyl)-piperazin-1-yl]-pentanoate

0.28 ml (0.003 mol) of acetic anhydride are added to a solution of 0.8 g (0.002 mol) of methyl 2-methyl-2-phenyl-5-[4-(4-amino-phenyl)-piperazin-1-yl]-pentanoate in 40 ml of acetic acid, the mixture is stirred for 14 hours at ambient temperature and then heated to 70°C for 4 hours. The solvent is distilled off using the rotary evaporator.

Yield: 0.5 g (56.3% of theory),

$C_{25}H_{33}N_3O_3$ (M = 423.56)

Calc.: molecular peak $(M)^+ = 423$

Found: molecular peak $(M)^+ = 423$

Example 24

Methyl 2-methyl-2-phenyl-5-[4-(4-methanesulphonylamino-phenyl)-piperazin-1-yl]-pentanoate

0.25 g (0.001 mol) of methanesulphonic acid anhydride are added to a solution of 0.5 g (0.001 mol) of methyl 2-methyl-2-phenyl-5-[4-(4-amino-phenyl)-piperazin-1-yl]-pentanoate in 20 ml of tetrahydrofuran and 1 ml (0.007 mol) of triethylamine while cooling with ice and the mixture is stirred for 14 hours at ambient temperature. The reaction mixture is poured onto water, extracted with ethyl acetate and dried over sodium sulphate. It is purified by column chromatography on silica gel (eluant: ethyl acetate).
Yield: 0.08 g (13.3% of theory),
$C_{24}H_{33}N_3O_4S$ (M = 459.61)

Calc.: molecular peak $(M)^+$ = 459

Found: molecular peak $(M)^+$ = 459

Example 25

Methyl 2-methyl-2-phenyl-5-[4-(3-ethoxycarbonyl-phenyl)-piperazin-1-yl]-pentanoate

Prepared analogously to Example 2 from 1-(3-ethoxycarbonyl-phenyl)-piperazine and methyl 5-bromo-2-methyl-2-phenyl-pentanoate.
Yield: 0.07 g (14.1 % of theory),
$C_{26}H_{34}N_2O_4$ (M = 438.57)

Calc.: molecular peak $(M+H)^+$ = 439

Found: molecular peak $(M+H)^+$ = 439

Example 26

Methyl 2-methyl-2-phenyl-5-[4-(4-methoxycarbonyl-phenyl)-piperazin-1-yl]-pentanoate

Prepared analogously to Example 2 from 1-(4-methoxycarbonyl-phenyl)-piperazine and methyl 5-bromo-2-methyl-2-phenyl-pentanoate.
Yield: 0.08 g (20.8 % of theory),
Melting point: 121-122°C
$C_{25}H_{32}N_2O_4$ (M = 424.54)

Calc.: molecular peak $(M+H)^+$ = 425

Found: molecular peak $(M+H)^+$ = 425

Example 27

Methyl 5-(4-biphenyl-4-yl-piperazin-1-yl)-2-methyl-2-phenyl-pentanoate

a. 1-Benzyl-4-biphenyl-4-yl-piperazine

1.6 ml (0.05 mol) of n-butyllithium solution in n-hexane is added dropwise to a solution of 8.81 g (0.05 mol) of 1-benzylpiperazine in 50 ml of anhydrous tetrahydrofuran under argon at 0°C and stirred for one hour. Then 9.21 g (0.05 mol) of 4-methoxybiphenyl are added and the reaction mixture is refluxed for 12 hours. The solvent is then evaporated off, the residue is combined with 150 ml of 2N hydrocholoric acid followed by diethyl ether and the precipitate formed is filtered off. The precipitate is washed with diethyl ether, suspended in 20% sodium carbonate solution and extracted several times with dichloromethane. After drying over magnesium sulphate the solvent is eliminated and the residue is washed with ethyl acetate and diethyl ether.

Yield: 12.5 g (85 % of theory),

Melting point: 146-148°C

b. 1-Biphenyl-4-yl-piperazine

A suspension of 12.45 g (0.037 mol) of 1-benzyl-4-biphenyl-4-yl-piperazine and 4 g of palladium hydroxide in 360 ml of methanol is stirred in a Parr apparatus for 6 hours at ambient temperature under a hydrogen pressure of 50 psi. The catalyst is separated off and the filtrate is evaporated down.

Yield: 8.64 g (95.6 % of theory),

Melting point: 134-138°C

c. Methyl 5-(4-biphenyl-4-yl-piperazin-1-yl)-2-methyl-2-phenyl-pentanoate

Prepared analogously to Example 2 from 1-biphenyl-4-yl-piperazine and methyl 5-bromo-2-methyl-2-phenyl-pentanoate.
Yield: 0.14 g (37.7 % of theory),
Melting point: 103°C
$C_{29}H_{34}N_2O_2$ (M = 442.60)
Calc.: molecular peak $(M)^+$ = 442
Found: molecular peak $(M)^+$ = 442

Example 28

Methyl 5-(4-biphenyl-3-yl-piperazin-1-yl)-2-methyl-2-phenyl-pentanoate

a. 1-Biphenyl-3-yl-piperazine-dihydrochloride
A suspension of 1 g (4.29 mmol) 3-bromobiphenyl, 2.2 g (25.54 mmol) of piperazine and 2.499 g (26 mmol) of sodium tert. butoxide in 40 ml of toluene is heated to 80°C under nitrogen. Then 0.01 g (0.011 mmol) of tris(dibenzylideneacetone)-dipalladium(0) and 0.02 g (0.032 mmol) of 2,2'-bis(diphenyl-phosphino)-1,1'-binaphthyl are added, the mixture is heated to 86 for 7 hours and stirred for 14 hours at ambient temperature. Water and ethyl acetate are added successively, the organic phase is separated off, dried over sodium sulphate and concentrated by evaporation. The residue is combined with an ethereal hydrochloric acid solution and diisopropyl ether and the precipitate formed is filtered off.
Yield: 1.05 g (78.6 % of theory),
Melting point: 219-221°C
$C_{16}H_{18}N_2$ (M = 238.34)
Calc.: molecular peak $(M+H)^+$ = 239
Found: molecular peak $(M+H)^+$ = 239

b. methyl 5-(4-biphenyl-3-yl-piperazin-1-yl)-2-methyl-2-phenyl-pentanoate

Prepared analogously to Example 2 from 1-biphenyl-3-yl-piperazine-dihydrochloride and methyl 5-bromo-2-methyl-2-phenyl-pentanoate.
Yield: 0.18 g (63.2 % of theory),
$C_{29}H_{34}N_2O_2$ (M = 442.60)

Calc.: molecular peak $(M+H)^+$ = 443

Found: molecular peak $(M+H)^+$ = 443

The following compounds may be prepared analogously to the method described in Example 32:

(1) ethyl 5-(4-biphenyl-4-yl-piperazin-1-yl)-2-methyl-2-phenyl-pentanoate

(2) propyl 5-(4-biphenyl-4-yl-piperazin-1-yl)-2-methyl-2-phenyl-pentanoate

(3) isopropyl 5-(4-biphenyl-4-yl-piperazin-1-yl)-2-methyl-2-phenyl-pentanoate

(4) ethyl 5-(4-biphenyl-3-yl-piperazin-1-yl)-2-methyl-2-phenyl-pentanoate

(5) propyl 5-(4-biphenyl-3-yl-piperazin-1-yl)-2-methyl-2-phenyl-pentanoate

(6) isopropyl 5-(4-biphenyl-3-yl-piperazin-1-yl)-2-methyl-2-phenyl-pentanoate

(7) methyl 5-[4-(4'-fluoro-biphenyl-4-yl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(8) ethyl 5-[4-(4'-fluoro-biphenyl-4-yl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(9) propyl 5-[4-(4'-fluoro-biphenyl-4-yl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(10) isopropyl 5-[4-(4'-fluoro-biphenyl-4-yl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(11) methyl 5-[4-(3'-fluoro-biphenyl-4-yl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(12) ethyl 5-[4-(3'-fluoro-biphenyl-4-yl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(13) propyl 5-[4-(3'-fluoro-biphenyl-4-yl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(14) isopropyl 5-[4-(3'-fluoro-biphenyl-4-yl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(15) methyl 5-[4-(2'-fluoro-biphenyl-4-yl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(16) ethyl 5-[4-(2'-fluoro-biphenyl-4-yl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(17) propyl 5-[4-(2'-fluoro-biphenyl-4-yl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(18) isopropyl 5-[4-(2'-fluoro-biphenyl-4-yl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(19) methyl 5-[4-(4'-chloro-biphenyl-4-yl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(20) ethyl 5-[4-(4'-chloro-biphenyl-4-yl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(21) propyl 5-[4-(4'-chloro-biphenyl-4-yl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(22) isopropyl 5-[4-(4'-chloro-biphenyl-4-yl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(23) methyl 5-[4-(3'-chloro-biphenyl-4-yl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(24) ethyl 5-[4-(3'-chloro-biphenyl-4-yl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(25) propyl 5-[4-(3'-chloro-biphenyl-4-yl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(26) isopropyl 5-[4-(3'-chloro-biphenyl-4-yl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(27) methyl 5-[4-(2'-chloro-biphenyl-4-yl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(28) ethyl 5-[4-(2'-chloro-biphenyl-4-yl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(29) propyl 5-[4-(2'-chloro-biphenyl-4-yl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(30) isopropyl 5-[4-(2'-chloro-biphenyl-4-yl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(31) methyl 5-[4-(4'-trifluoromethyl-biphenyl-4-yl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(32) ethyl 5-[4-(4'-trifluoromethyl-biphenyl-4-yl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(33) propyl 5-[4-(4'-trifluoromethyl-biphenyl-4-yl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(34) isopropyl 5-[4-(4'-trifluoromethyl-biphenyl-4-yl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(35) 5 methyl -[4-(3'-trifluoromethyl-biphenyl-4-yl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(36) ethyl 5-[4-(3'-trifluoromethyl-biphenyl-4-yl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(37) propyl 5-[4-(3'-trifluoromethyl-biphenyl-4-yl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(38) isopropyl 5-[4-(3'-trifluoromethyl-biphenyl-4-yl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(39) methyl 5-[4-(2'-trifluoromethyl-biphenyl-4-yl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(40) ethyl 5-[4-(2'-trifluoromethyl-biphenyl-4-yl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(41) propyl 5-[4-(2'-trifluoromethyl-biphenyl-4-yl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(42) isopropyl 5-[4-(2'-trifluoromethyl-biphenyl-4-yl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(43) methyl 5-[4-(4'-methyl-biphenyl-4-yl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(44) ethyl 5-[4-(4'-methyl-biphenyl-4-yl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(45) propyl 5-[4-(4'-methyl-biphenyl-4-yl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(46) isopropyl 5-[4-(4'-methyl-biphenyl-4-yl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(47) methyl 5-[4-(3'-methyl-biphenyl-4-yl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(48) ethyl 5-[4-(3'-methyl-biphenyl-4-yl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(49) propyl 5-[4-(3'-methyl-biphenyl-4-yl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(50) isopropyl 5-[4-(3'-methyl-biphenyl-4-yl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(51) methyl 5-[4-(2'-methyl-biphenyl-4-yl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(52) ethyl 5-[4-(2'-methyl-biphenyl-4-yl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(53) propyl 5-[4-(2'-methyl-biphenyl-4-yl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(54) isopropyl 5-[4-(2'-methyl-biphenyl-4-yl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(55) methyl 5-[4-(4'-methoxy-biphenyl-4-yl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(56) ethyl 5-[4-(4'-methoxy-biphenyl-4-yl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(57) propyl 5-[4-(4'-methoxy-biphenyl-4-yl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(58) isopropyl 5-[4-(4'-methoxy-biphenyl-4-yl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(59) methyl 5-[4-(3'-methoxy-biphenyl-4-yl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(60) ethyl 5-[4-(3'-methoxy-biphenyl-4-yl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(61) propyl 5-[4-(3'-methoxy-biphenyl-4-yl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(62) isopropyl 5-[4-(3'-methoxy-biphenyl-4-yl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(63) methyl 5-[4-(2'-methoxy-biphenyl-4-yl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(64) ethyl 5-[4-(2'-methoxy-biphenyl-4-yl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(65) propyl 5-[4-(2'-methoxy-biphenyl-4-yl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(66) isopropyl 5-[4-(2'-methoxy-biphenyl-4-yl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(67) methyl 5-[4-(4'-fluoro-biphenyl-3-yl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(68) ethyl 5-[4-(4'-fluoro-biphenyl-3-yl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(69) propyl 5-[4-(4'-fluoro-biphenyl-3-yl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(70) isopropyl 5-[4-(4'-fluoro-biphenyl-3-yl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(71) methyl 5-[4-(3'-fluoro-biphenyl-3-yl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(72) ethyl 5-[4-(3'-fluoro-biphenyl-3-yl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(73) propyl 5-[4-(3'-fluoro-biphenyl-3-yl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(74) isopropyl 5-[4-(3'-fluoro-biphenyl-3-yl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(75) methyl 5-[4-(2'-fluoro-biphenyl-3-yl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(76) ethyl 5-[4-(2'-fluoro-biphenyl-3-yl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(77) propyl 5-[4-(2'-fluoro-biphenyl-3-yl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(78) isopropyl 5-[4-(2'-fluoro-biphenyl-3-yl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(79) methyl 5-[4-(4'-chloro-biphenyl-3-yl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(80) ethyl 5-[4-(4'-chloro-biphenyl-3-yl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(81) propyl 5-[4-(4'-chloro-biphenyl-3-yl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(82) isopropyl 5-[4-(4'-chloro-biphenyl-3-yl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(83) methyl 5-[4-(3'-chloro-biphenyl-3-yl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(84) ethyl 5-[4-(3'-chloro-biphenyl-3-yl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(85) propyl 5-[4-(3'-chloro-biphenyl-3-yl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(86) isopropyl 5-[4-(3'-chloro-biphenyl-3-yl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(87) methyl 5-[4-(2'-chloro-biphenyl-3-yl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(88) ethyl 5-[4-(2'-chloro-biphenyl-3-yl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(89) propyl 5-[4-(2'-chloro-biphenyl-3-yl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(90) isopropyl 5-[4-(2'-chloro-biphenyl-3-yl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(91) methyl 5-[4-(4'-trifluoromethyl-biphenyl-3-yl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(92) ethyl 5-[4-(4'-trifluoromethyl-biphenyl-3-yl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(93) propyl 5-[4-(4'-trifluoromethyl-biphenyl-3-yl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(94) isopropyl 5-[4-(4'-trifluoromethyl-biphenyl-3-yl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(95) methyl 5-[4-(3'-trifluoromethyl-biphenyl-3-yl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(96) ethyl 5-[4-(3'-trifluoromethyl-biphenyl-3-yl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(97) propyl 5-[4-(3'-trifluoromethyl-biphenyl-3-yl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(98) isopropyl 5-[4-(3'-trifluoromethyl-biphenyl-3-yl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(99) methyl 5-[4-(2'-trifluoromethyl-biphenyl-3-yl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(100) ethyl 5-[4-(2'-trifluoromethyl-biphenyl-3-yl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(101) propyl 5-[4-(2'-trifluoromethyl-biphenyl-3-yl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(102) isopropyl 5-[4-(2'-trifluoromethyl-biphenyl-3-yl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(103) methyl 5-[4-(4'-methyl-biphenyl-3-yl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(104) ethyl 5-[4-(4'-methyl-biphenyl-3-yl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(105) propyl 5-[4-(4'-methyl-biphenyl-3-yl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(106) isopropyl 5-[4-(4'-methyl-biphenyl-3-yl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(107) methyl 5-[4-(3'-methyl-biphenyl-3-yl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(108) ethyl 5-[4-(3'-methyl-biphenyl-3-yl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(109) propyl 5-[4-(3'-methyl-biphenyl-3-yl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(110) isopropyl 5-[4-(3'-methyl-biphenyl-3-yl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(111) methyl 5-[4-(2'-methyl-biphenyl-3-yl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(112) ethyl 5-[4-(2'-methyl-biphenyl-3-yl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(113) propyl 5-[4-(2'-methyl-biphenyl-3-yl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(114) isopropyl 5-[4-(2'-methyl-biphenyl-3-yl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(115) methyl 5-[4-(4'-methoxy-biphenyl-3-yl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(116) ethyl 5-[4-(4'-methoxy-biphenyl-3-yl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(117) propyl 5-[4-(4'-methoxy-biphenyl-3-yl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(118) isopropyl 5-[4-(4'-methoxy-biphenyl-3-yl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(119) methyl 5-[4-(3'-methoxy-biphenyl-3-yl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(120) ethyl 5-[4-(3'-methoxy-biphenyl-3-yl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(121) propyl 5-[4-(3'-methoxy-biphenyl-3-yl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(122) isopropyl 5-[4-(3'-methoxy-biphenyl-3-yl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(123) methyl 5-[4-(2'-methoxy-biphenyl-3-yl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(124) ethyl 5-[4-(2'-methoxy-biphenyl-3-yl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(125) propyl 5-[4-(2'-methoxy-biphenyl-3-yl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(126) isopropyl 5-[4-(2'-methoxy-biphenyl-3-yl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(127) methyl 5-[4-(3-thiazol-2-yl-phenyl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(128) methyl 5-[4-(3-thiophen-3-yl-phenyl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(129) methyl 5-{4-[3-(1H-imidazol-4-yl)-phenyl]-piperazin-1-yl}-2-methyl-2-phenyl-pentanoate

(130) methyl 5-{4-[3-(1H-pyrrol-2-yl)-phenyl]-piperazin-1-yl}-2-methyl-2-phenyl-pentanoate

(131) methyl 5-{4-[3-(1H-benzoimidazol-2-yl)-phenyl]-piperazin-1-yl}-2-methyl-2-phenyl-pentanoate

(132) methyl 5-[4-(4-thiazol-2-yl-phenyl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(133) methyl 5-[4-(4-thiophen-3-yl-phenyl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(134) methyl 5-{4-[4-(1H-imidazol-4-yl)-phenyl]-piperazin-1-yl}-2-methyl-2-phenyl-pentanoate

(135) methyl 5-{4-[4-(1H-pyrrol-2-yl)-phenyl]-piperazin-1-yl}-2-methyl-2-phenyl-pentanoate

(136) methyl 5-{4-[4-(1H-benzoimidazol-2-yl)-phenyl]-piperazin-1-yl}-2-methyl-2-phenyl-pentanoate

(137) methyl 5-[4-(4-pyridin-2-yl-phenyl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(138) methyl 5-[4-(4-pyridin-2-yl-phenyl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(139) methyl 5-[4-(6-phenyl-pyridin-2-yl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(140) methyl 5-[4-(4-phenyl-pyrimidin-2-yl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(141) methyl 5-[4-(2-phenyl-pyrimidin-5-yl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(142) methyl 5-[4-(5-phenyl-pyridin-2-yl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(143) methyl 5-[4-(5-phenyl-thiophen-2-yl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(144) methyl 5-[4-(5-phenyl-oxazol-2-yl)-piperazin-1-yl]-2-methyl-2-phenyl-pentanoate

(145) methyl 5-(4-[2,2']bipyridinyl-6-yl-piperazin-1-yl)-2-methyl-2-phenyl-pentanoate

(146) methyl 5-(4-biphenyl-4-yl-piperazin-1-yl)-2-methyl-2-(4-fluoro-phenyl)-pentanoate

(147) methyl 5-(4-biphenyl-3-yl-piperazin-1-yl)-2-methyl-2-(4-fluorophenyl)-pentanoate

Example 29

Methyl 2-ethyl-2-phenyl-5-(4-phenyl-piperazin-1-yl)-pentanoate

a. methyl 2-phenylbutanecarboxylate

15 g (0.091 mol) of 2-phenylbutanecarboxylic acid are dissolved in 150 ml of methanolic hydrochloric acid and stirred for 18 hours at ambient temperature. The solvent is removed and the residue is extracted with ethyl acetate and saturated sodium hydrogen carbonate solution. The organic phases are extracted with water and saturated saline solution, dried over magnesium sulphate and evaporated down.

Yield: 14.4 g (88.8 % of theory),

$C_{11}H_{14}O_2$ (M = 178.23)

Calc.: molecular peak $(M+Na)^+$ = 201

Found: molecular peak $(M+Na)^+$ = 201

b. methyl 5-bromo-2-ethyl-2-phenyl-pentanoate

15 g of n-butyllithium (0.081 mol) as a 2.5-molar solution in hexane are added dropwise to a solution of 11.35 ml (0.081 mol) of diisopropylamine in 200 ml of anhydrous tetrahydrofuran at -30°C and the mixture is stirred for 10 minutes at -10°C. At -76°C 14.4 g (0.081 mol) of methyl 2-phenylbutanecarboxylate are added dropwise and the mixture is stirred for 30 minutes at this temperature. Then 8.62 ml (0.085 mol) of 1,3-dibromopropane are added, once it has all been added the cooling bath is removed and the mixture is stirred for 14 hours at ambient temperature. The reaction solution is poured onto 1.2 l of water and extracted with diethylether. The organic phases are extracted with water, dried over sodium sulphate and the solvent is eliminated. The residue is distilled under a high vacuum.

Yield: 10.1 g (41.7 % of theory),

Boiling point: 127°C at 0.22 mbar

c. methyl 2-ethyl-2-phenyl-5-(4-phenyl-piperazin-1-yl)-pentanoate

0.2 g (1.23 mmol) of 1-phenylpiperazine, 0.33 g (1.1 mmol) of ethyl 5-bromo-2-ethyl-2-phenyl-pentanoate and 0.166 g (1.2 mmol) of potassium carbonate are dissolved in 20 ml of acetonitrile. The mixture is stirred for 8 hours at 60°C and for 14 hours at ambient temperature. Then the reaction mixture is poured onto water and extracted with ethyl acetate. The organic phase is dried over sodium sulphate and the solvent is distilled off using the rotary evaporator. After column chromatography on silica gel (eluant: dichloromethane/methanol = 20:1) a yellow oil remains.

Yield: 0.336 g (71.6 % of theory),

$C_{24}H_{32}N_2O_2$ (M = 380.53)

Calc.: molecular peak $(M+H)^+$ = 381

Found: molecular peak $(M+H)^+$ = 381

Example 30

Methyl 2-ethyl-2-phenyl-5-[4-(4-chloro-phenyl)-piperazin-1-yl]-pentanoate

Prepared analogously to Example 2 from 1-(4-chloro-phenyl)-piperazine and methyl 5-bromo-2-ethyl-2-phenyl-pentanoate.

Yield: 0,76 g (45.8 % of theory),

$C_{24}H_{31}ClN_2O_2$ (M = 414.98)

Calc.: molecular peak $(M)^+$ = 414/416

Found: molecular peak $(M)^+$ = 414/416

Example 31

Methyl 5-(4-biphenyl-4-yl-piperazin-1-yl)-2-ethyl-2-phenyl-pentanoate

Prepared analogously to Example 2 from 1-biphenyl-4-yl-piperazine and methyl 5-bromo-2-ethyl-2-phenyl-pentanoate.

Yield: 0.4 g (54.7 % of theory),

$C_{30}H_{36}N_2O_2$ (M = 456.63)

Melting point: 84-87°C

Calc.: molecular peak $(M)^+$ = 456

Found: molecular peak $(M)^+$ = 456

Example 32

Methyl 5-[4-(3'-trifluoromethyl-biphenyl-3-yl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

a. tert.butyl 4-(3-bromo-phenyl)-piperazine-1-carboxylate

6 ml (0.043 mol) of triethylamine and 5 g (0.023 mol) of pivalic anhydride are added to a solution of 5.1 g (0.021 mol) of 1-(3-bromo-phenyl)-piperazine in 80 ml of tetrahydrofuran. The reaction solution is stirred for 3 hours at 60°C. Then it is poured onto water, extracted with ethyl acetate and the organic phase is dried over sodium sulphate. A yellow oil remains.

b. tert. butyl 4-(3'-trifluoromethyl-biphenyl-3-yl)-piperazine-1-carboxylate

A suspension of 1.5 g (4.39 mmol) of tert.butyl 4-(3-bromo-phenyl)-piperazine-1-carboxylate, 0.93 g (4.89 mmol) of 3-trifluoroboric acid, 0.05 g (0.22 mmol) of palladium acetate, 1.64 g (4.4 mmol) of tetrabutylammonium iodide and 1.2 g (10.71 mmol) of potassium tert, butoxide in 15 ml of water is refluxed for 5 hours under nitrogen. Then the solvent is distilled off. The misture is purified by column chromatography on silica gel (eluant: cyclohexane/ethyl acetate = 4:1).

Yield: 0.75 g (42 % of theory),

$C_{22}H_{25}F_3N_2O_2$ (M= 406.45)

Melting point: 104°C

Calc.: molecular peak $(M+H)^+$ = 407

Found: molecular peak $(M+H)^+$ = 407

c. 1-(3'-trifluoromethyl-biphenyl-3-yl)-piperazine

A solution of 0.7 g (1.72 mmol) of tert.butyl 4-(3'-trifluoromethyl-biphenyl-3-yl)-piperazine-1-carboxylate and 3 ml of trifluoroacetic acid in 70 ml of dichloromethane is stirred for 14 hours at ambient temperature. Then the solvent is distilled off, the residue is made alkaline with 2N sodium hydroxide solution and extracted with ethyl acetate. The organic phase is dried over sodium sulphate.
Yield: 0.31 g (58.5 % of theory),
$C_{17}H_{17}F_3N_2$ (M = 306.34)

Melting point: 87°C

Calc.: molecular peak $(M+H)^+$ = 307

Found: molecular peak $(M+H)^+$ = 307

d. methyl 5-[4-(3'-trifluoromethyl-biphenyl-3-yl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

Prepared analogously to Example 2a from 1-(3'-trifluoromethyl-biphenyl-3-yl)-piperazine, methyl 5-bromo-2-ethyl-2-phenyl-pentanoate and dimethylformamide.
Yield: 0,.3 g (24.7 % of theory),
$C_{31}H_{35}F_3N_2O_2$ (M= 524.63)

Calc.: molecular peak $(M+H)^+$ = 525

Found: molecular peak $(M+H)^+$ = 525

Example 33

Methyl 5-(4-biphenyl-3-yl-piperazin-1-yl)-2-ethyl-2-phenyl-pentanoate

Prepared analogously to Example 2 from 1-biphenyl-3-yl-piperazine-dihydrochloride and methyl 5-bromo-2-ethyl-2-phenyl-pentanoate.
Yield: 0.6 g (81.8 % of theory),
$C_{30}H_{36}N_2O_2$ (M = 456.63)

Calc.: molecular peak $(M)^+$ = 456

Found: molecular peak $(M)^+$ = 456

The following compounds may be prepared using the method described in Example 32:

(1) ethyl 5-[4-(4-chloro-phenyl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(2) propyl 5-[4-(4-chloro-phenyl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(3) isopropyl 5-[4-(4-chloro-phenyl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(4) ethyl 5-(4-biphenyl-4-yl-piperazin-1-yl)-2-ethyl-2-phenyl-pentanoate

(5) propyl 5-(4-biphenyl-4-yl-piperazin-1-yl)-2-ethyl-2-phenyl-pentanoate

(6) isopropyl 5-(4-biphenyl-4-yl-piperazin-1-yl)-2-ethyl-2-phenyl-pentanoate

(7) ethyl 5-(4-biphenyl-3-yl-piperazin-1-yl)-2-ethyl-2-phenyl-pentanoate

(8) propyl 5-(4-biphenyl-3-yl-piperazin-1-yl)-2-ethyl-2-phenyl-pentanoate

(9) isopropyl 5-(4-biphenyl-3-yl-piperazin-1-yl)-2-ethyl-2-phenyl-pentanoate

(10) methyl 5-[4-(4'-fluoro-biphenyl-4-yl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(11) ethyl 5-[4-(4'-fluoro-biphenyl-4-yl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(12) propyl 5-[4-(4'-fluoro-biphenyl-4-yl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(13) isopropyl 5-[4-(4'-fluoro-biphenyl-4-yl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(14) methyl 5-[4-(3'-fluoro-biphenyl-4-yl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(15) ethyl 5-[4-(3'-fluoro-biphenyl-4-yl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(16) propyl 5-[4-(3'-fluoro-biphenyl-4-yl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(17) isopropyl 5-[4-(3'-fluoro-biphenyl-4-yl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(18) methyl 5-[4-(2'-fluoro-biphenyl-4-yl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(19) ethyl 5-[4-(2'-fluoro-biphenyl-4-yl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(20) propyl 5-[4-(2'-fluoro-biphenyl-4-yl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(21) isopropyl 5-[4-(2'-fluoro-biphenyl-4-yl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(22) methyl 5-[4-(4'-chloro-biphenyl-4-yl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(23) ethyl 5-[4-(4'-chloro-biphenyl-4-yl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(24) propyl 5-[4-(4'-chloro-biphenyl-4-yl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(25) isopropyl 5-[4-(4'-chloro-biphenyl-4-yl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(26) methyl 5-[4-(3'-chloro-biphenyl-4-yl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(27) ethyl 5-[4-(3'-chloro-biphenyl-4-yl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(28) propyl 5-[4-(3'-chloro-biphenyl-4-yl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(29) isopropyl 5-[4-(3'-chloro-biphenyl-4-yl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(30) methyl 5-[4-(2'-chloro-biphenyl-4-yl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(31) ethyl 5-[4-(2'-chloro-biphenyl-4-yl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(32) propyl 5-[4-(2'-chloro-biphenyl-4-yl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(33) isopropyl 5-[4-(2'-chloro-biphenyl-4-yl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(34) methyl 5-[4-(4'-trifluoromethyl-biphenyl-4-yl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(35) ethyl 5-[4-(4'-trifluoromethyl-biphenyl-4-yl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(36) propyl 5-[4-(4'-trifluoromethyl-biphenyl-4-yl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(37) isopropyl 5-[4-(4'-trifluoromethyl-biphenyl-4-yl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(38) methyl 5-[4-(3'-trifluoromethyl-biphenyl-4-yl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(39) ethyl 5-[4-(3'-trifluoromethyl-biphenyl-4-yl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(40) propyl 5-[4-(3'-trifluoromethyl-biphenyl-4-yl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(41) isopropyl 5-[4-(3'-trifluoromethyl-biphenyl-4-yl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(42) methyl 5-[4-(2'-trifluoromethyl-biphenyl-4-yl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(43) ethyl 5-[4-(2'-trifluoromethyl-biphenyl-4-yl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(44) propyl 5-[4-(2'-trifluoromethyl-biphenyl-4-yl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(45) isopropyl 5-[4-(2'-trifluoromethyl-biphenyl-4-yl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(46) methyl 5-[4-(4'-methyl-biphenyl-4-yl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(47) ethyl 5-[4-(4'-methyl-biphenyl-4-yl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(48) propyl 5-[4-(4'-methyl-biphenyl-4-yl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(49) isopropyl 5-[4-(4'-methyl-biphenyl-4-yl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(50) methyl 5-[4-(3'-methyl-biphenyl-4-yl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(51) ethyl 5-[4-(3'-methyl-biphenyl-4-yl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(52) propyl 5-[4-(3'-methyl-biphenyl-4-yl)-piperazin-1-yl]-2-ethyl-2- phenyl-pentanoate

(53) isopropyl 5-[4-(3'-methyl-biphenyl-4-yl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(54) methyl 5-[4-(2'-methyl-biphenyl-4-yl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(55) ethyl 5-[4-(2'-methyl-biphenyl-4-yl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(56) propyl 5-[4-(2'-methyl-biphenyl-4-yl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(57) isopropyl 5-[4-(2'-methyl-biphenyl-4-yl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(58) methyl 5-[4-(4'-methoxy-biphenyl-4-yl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(59) ethyl 5-[4-(4'-methoxy-biphenyl-4-yl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(60) propyl 5-[4-(4'-methoxy-biphenyl-4-yl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(61) isopropyl 5-[4-(4'-methoxy-biphenyl-4-yl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(62) methyl 5-[4-(3'-methoxy-biphenyl-4-yl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(63) ethyl 5-[4-(3'-methoxy-biphenyl-4-yl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(64) propyl 5-[4-(3'-methoxy-biphenyl-4-yl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(65) isopropyl 5-[4-(3'-methoxy-biphenyl-4-yl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(66) methyl 5-[4-(2'-methoxy-biphenyl-4-yl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(67) ethyl 5-[4-(2'-methoxy-biphenyl-4-yl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(68) propyl 5-[4-(2'-methoxy-biphenyl-4-yl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(69) isopropyl 5-[4-(2'-methoxy-biphenyl-4-yl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(70) methyl 5-[4-(4'-fluoro-biphenyl-3-yl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(71) ethyl 5-[4-(4'-fluoro-biphenyl-3-yl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(72) propyl 5-[4-(4'-fluoro-biphenyl-3-yl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(73) isopropyl 5-[4-(4'-fluoro-biphenyl-3-yl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(74) methyl 5-[4-(3'-fluoro-biphenyl-3-yl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(75 ethyl) 5-[4-(3'-fluoro-biphenyl-3-yl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(76) propyl 5-[4-(3'-fluoro-biphenyl-3-yl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(77) isopropyl 5-[4-(3'-fluoro-biphenyl-3-yl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(78) methyl 5-[4-(2'-fluoro-biphenyl-3-yl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(79) ethyl 5-[4-(2'-fluoro-biphenyl-3-yl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(80) propyl 5-[4-(2'-fluoro-biphenyl-3-yl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(81) isopropyl 5-[4-(2'-fluoro-biphenyl-3-yl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(82) methyl 5-[4-(4'-chloro-biphenyl-3-yl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(83) ethyl 5-[4-(4'-chloro-biphenyl-3-yl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(84) propyl 5-[4-(4'-chloro-biphenyl-3-yl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(85) isopropyl 5-[4-(4'-chloro-biphenyl-3-yl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(86) methyl 5-[4-(3'-chloro-biphenyl-3-yl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(87) ethyl 5-[4-(3'-chloro-biphenyl-3-yl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(88) propyl 5-[4-(3'-chloro-biphenyl-3-yl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(89) isopropyl 5-[4-(3'-chloro-biphenyl-3-yl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(90) methyl 5-[4-(2'-chloro-biphenyl-3-yl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(91) ethyl 5-[4-(2'-chloro-biphenyl-3-yl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(92) propyl 5-[4-(2'-chloro-biphenyl-3-yl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(93) isopropyl 5-[4-(2'-chloro-biphenyl-3-yl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(94) methyl 5-[4-(4'-trifluoromethyl-biphenyl-3-yl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(95) ethyl 5-[4-(4'-trifluoromethyl-biphenyl-3-yl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(96) propyl 5-[4-(4'-trifluoromethyl-biphenyl-3-yl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(97) isopropyl 5-[4-(4'-trifluoromethyl-biphenyl-3-yl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(98) ethyl 5-[4-(3'-trifluoromethyl-biphenyl-3-yl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(99) propyl 5-[4-(3'-trifluoromethyl-biphenyl-3-yl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(100) isopropyl 5-[4-(3'-trifluoromethyl-biphenyl-3-yl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(101) methyl 5-[4-(2'-trifluoromethyl-biphenyl-3-yl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(102) ethyl 5-[4-(2'-trifluoromethyl-biphenyl-3-yl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(103) propyl 5-[4-(2'-trifluoromethyl-biphenyl-3-yl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(104) isopropyl 5-[4-(2'-trifluoromethyl-biphenyl-3-yl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(105) methyl 5-[4-(4'-methyl-biphenyl-3-yl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(106) ethyl 5-[4-(4'-methyl-biphenyl-3-yl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(107) propyl 5-[4-(4'-methyl-biphenyl-3-yl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(108) isopropyl 5-[4-(4'-methyl-biphenyl-3-yl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(109) methyl 5-[4-(3'-methyl-biphenyl-3-yl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(110) ethyl 5-[4-(3'-methyl-biphenyl-3-yl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(111) propyl 5-[4-(3'-methyl-biphenyl-3-yl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(112) isopropyl 5-[4-(3'-methyl-biphenyl-3-yl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(113) methyl 5-[4-(2'-methyl-biphenyl-3-yl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(114) ethyl 5-[4-(2'-methyl-biphenyl-3-yl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(115) propyl 5-[4-(2'-methyl-biphenyl-3-yl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(116) isopropyl 5-[4-(2'-methyl-biphenyl-3-yl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(117) methyl 5-[4-(4'-methoxy-biphenyl-3-yl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(118) ethyl 5-[4-(4'-methoxy-biphenyl-3-yl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(119) propyl 5-[4-(4'-methoxy-biphenyl-3-yl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(120) isopropyl 5-[4-(4'-methoxy-biphenyl-3-yl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(121) methyl 5-[4-(3'-methoxy-biphenyl-3-yl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(122) ethyl 5-[4-(3'-methoxy-biphenyl-3-yl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(123) propyl 5-[4-(3'-methoxy-biphenyl-3-yl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(124) isopropyl 5-[4-('-methoxy-biphenyl-3-yl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(125) methyl 5-[4-(2'-methoxy-biphenyl-3-yl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(126) ethyl 5-[4-(2'-methoxy-biphenyl-3-yl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(127) propyl 5-[4-(2'-methoxy-biphenyl-3-yl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(128) isopropyl 5-[4-(2'-methoxy-biphenyl-3-yl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(129) methyl 5-[4-(3-thiazol-2-yl-phenyl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(130) methyl 5-[4-(3-thiophen-3-yl-phenyl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(131) methyl 5-{4-[3-(1H-imidazol-4-yl)-phenyl]-piperazin-1-yl}-2-ethyl-2-phenyl-pentanoate

(132) methyl 5-{4-[3-(1H-pyrrol-2-yl)-phenyl]-piperazin-1-yl}-2-ethyl-2-phenyl-pentanoate

(133) methyl 5-{4-[3-(1H-benzoimidazol-2-yl)-phenyl]-piperazin-1-yl}-2-ethyl-2-phenyl-pentanoate

(134) methyl 5-[4-(4-thiazol-2-yl-phenyl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(135) methyl 5-[4-(4-thiophen-3-yl-phenyl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(136) methyl 5-{4-[4-(1H-imidazol-4-yl)-phenyl]-piperazin-1-yl}-2-ethyl-2-phenyl-pentanoate

(137) methyl 5-{4-[4-(1H-pyrrol-2-yl)-phenyl]-piperazin-1-yl}-2-ethyl-2-phenyl-pentanoate

(138) methyl 5-{4-[4-(1H-benzoimidazol-2-yl)-phenyl]-piperazin-1-yl}-2-ethyl-2-phenyl-pentanoate

(139) methyl 5-[4-(4-pyridin-2-yl-phenyl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(140) methyl 5-[4-(6-phenyl-pyridin-2-yl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(141) methyl 5-[4-(4-phenyl-pyrimidin-2-yl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(142) methyl 5-[4-(2-phenyl-pyrimidin-5-yl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(143) methyl 5-[4-(5-phenyl-pyridin-2-yl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(144) methyl 5-[4-(5-phenyl-thiophen-2-yl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(145) methyl 5-[4-(5-phenyl-oxazol-2-yl)-piperazin-1-yl]-2-ethyl-2-phenyl-pentanoate

(146) methyl 5-(4-[2,2']bipyridinyl-6-yl-piperazin-1-yl)-2-ethyl-2-phenyl-pentanoate

(147) methyl 5-(4-biphenyl-4-yl-piperazin-1-yl)-2-ethyl-2-(4-fluoro-phenyl)-pentanoate

(148) methyl 5-(4-biphenyl-3-yl-piperazin-1-yl)-2-ethyl-2-(4-fluoro-phenyl)-pentanoate

Example 34

Methyl 2,2-diphenyl-5-(4-phenyl-piperazin-1-yl)-pentanoate

a. 3.3-Diphenyl-tetrahydro-pyran-2-one

33 ml (0.053 mol) of a 1.6-molar n-butyllithium solution in hexane is slowly added dropwise to a solution of 5 g (0.024 mol) of diphenylacetic acid in 50 ml of tetrahydrofuran under nitrogen at -10°C and stirred for 30 minutes at 0°C. Then 3 ml (0.03 mol) of 1,3-dibromopropane are added at 0°C, the mixture is stirred for 30 minutes at 0°C and for 14 hours at ambient temperature. 10 ml of water are added to the reaction mixture which is then evaporated down. The residue is suction filtered and washed with water.

Yield: 4.11 g (67.9 % of theory),

Melting point: 110-113°C

$C_{17}H_{16}O_2$ (M = 252.31)

Calc.: molecular peak (M^+) = 252

Found: molecular peak (M^+) = 252

b. 5-bromo-2.2-diphenyl-pentanoic acid

A suspension of 2.8 g (0.011 mol) of 3,3-diphenyl-tetrahydro-pyran-2-one in 30 ml (0.267 mol) of hydrogen bromide solution is heated to 160°C for 3 hours and the hydrobromic acid solution is distilled off in a water jet vacuum at this temperature.

Yield: 3.5 g (95.5 % of theory)

c. methyl 5-bromo-2.2-diphenyl-pentanoate

A suspension of 3 g (0.009 mol) of 5-bromo-2,2-diphenyl-pentanoic acid in 30 ml of thionyl chloride is refluxed for 3 hours, after which time a solution is formed. The excess thionylchloride is distilled off in a water jet vacuum. The residue is mixed with 90 ml of methanol and refluxed for 3 hours. Then it is evaporated to dryness.

Yield: 2.14 g (68.5 % of theory)

d. methyl 2,2-diphenyl-5-(4-phenyl-piperazin-1-yl)-pentanoate

A solution of 0.3 g (0.002 mol) of 1-phenylpiperazine, 0.32 g (0.001 mol) of methyl 5-bromo-2,2-diphenyl-pentanoate and 1 ml (0.007 mol) of triethylamine in 10 ml of acetonitrile are stirred for 14 hours at ambient temperature. The reaction solution is then concentrated by evaporation, taken up in dichloromethane, extracted with water and the organic phase is dried over sodium sulphate.

Yield: 0.33 g (77 % of theory),

$C_{28}H_{32}N_2O_2$ (M = 428.57)

Calc.: molecular peak $(M+H)^+$ = 429

Found: molecular peak $(M+H)^+$ = 429

Example 35

2-Ethyl-2-phenyl-5-(4-phenyl-piperazin-1-yl)-pentanoic acid

A suspension of 0.5 g (1.78 mmol) of methyl 2-ethyl-2-phenyl-5-(4-phenyl-piperazin-1-yl)-pentanoate in 50 ml of 6N hydrochloric acid is refluxed for 14 hours. Then the mixture is neutralised with saturated sodium hydrogen carbonate solution, extracted with ethyl acetate and evaporated down. Colourless crystals remain.

Yield: 0.19 g (51.8 % of theory),

Melting point: 219-222°C

$C_{23}H_{30}N_2O_2$ (M = 366.50)

Calc.: molecular peak $(M)^+$ = 366

Found: molecular peak $(M)^+$ = 366

Example 36

5-(4-biphenyl-3-yl-piperazin-1-yl)-2-methyl-2-phenyl-pentanoic acid-dihydrochloride

A suspension of 0.6 g (1.35 mmol) of methyl 5-(4-biphenyl-3-yl-piperazin-1-yl)-2-methyl-2-phenyl-pentanoate in 50 ml of 6N hydrochloric acid is refluxed for 4 hours. Then the reaction mixture is poured onto water, the precipitate is filtered off and washed with water. Beige crystals remain.

Yield: 0.4 g (58.8 % of theory),

Melting point: 225-227°C

$C_{28}H_{32}N_2O_2$ (M = 428.57)

Calc.: molecular peak $(M+H)^+$ = 429

Found: molecular peak $(M+H)^+$ = 429

Example 37

Methyl 2-methyl-2-phenyl-5-(4-phenyl-piperazin-1-yl)-hexanecarboxylate

a. methyl 6-bromo-2-ethyl-2-phenyl-hexanecarboxylate

40 ml (0.1 mol) of n-butyllithium as a 2.5-molar solution in hexane are added dropwise to a solution of 14 ml (0.1 mol) of diisopropylamine in 150 ml of anhydrous tetrahydrofuran at -30°C and stirred for ten minutes at -10°C. At -76°C 16.4 g (0.1 mol) of methyl 2-phenylbutanecarboxylate are added dropwise and stirred for 30 minutes at this temperature. Then 12.12 ml (0.101 mol) of 1,3-dibromobutane are added, once all has been added the cooling bath is taken away and the mixture is stirred for 14 hours at ambient temperature. The reaction solution is poured onto 1.2 l of water and extracted with diethylether. The organic phases are extracted with water, dried over sodium sulphate and the solvent is eliminated. The residue is distilled off under a high vacuum.

Yield: 15.8 g (52.8 % of theory),

Boiling point: 100-117°C at 0.17 mbar

$C_{14}H_{19}BrO_2$ (M = 299.21)

Calc.: molecular peak $(M+Na)^+$ = 321/23

Found: molecular peak $(M+Na)^+$ = 321/23

b. methyl 2-methyl-2-phenyl-5-(4-phenyl-piperazin-1-yl)-hexanecarboxylate

Prepared analogously to Example 2 from 1-phenyl-piperazine and methyl 6-bromo-2-methyl-2-phenyl-hexanecarboxylate.

Yield: 0.17 g (36.2 % of theory),

$C_{24}H_{32}N_2O_2$ (M = 380.53)

Calc.: molecular peak $(M+H)^+$ = 381

Found: molecular peak $(M+H)^+$ = 381

Example 38

Tablets containing 5 mg of active substance per tablet

Composition:

active substance	5.0 mg
lactose monohydrate	70.8 mg
microcrystalline cellulose	40.0 mg
sodium carboxymethylcellulose, insolubly crosslinked	3.0 mg
magnesium stearate	1.2 mg

Preparation:

The active substance is mixed for 15 minutes with lactose monohydrate, microcrystalline cellulose and sodium carboxymethylcellulose in a suitable diffusion mixer. Magnesium stearate is added and mixed with the other substances for another 3 minutes.

The finished mixture is compressed in a tablet press to form facetted flat round tablets.

Diameter of the tablet: 7 mm
Weight of a tablet: 120 mg

Example 39

Capsules containing 50 mg of active substance per capsule

Composition:

active substance	50.0 mg
lactose monohydrate	130.0 mg
corn starch	65.0 mg
highly dispersed silicon dioxide	2.5 mg
magnesium stearate	2.5 mg

Preparation:

A starch paste is prepared by swelling some of the corn starch in a suitable amount of hot water. The paste is then left to cool to room temperature.

The active substance is premixed for 15 minutes in a suitable mixer with lactose monohydrate and corn starch. The starch paste is added and the mixture is mixed with sufficient water to produce a moist homogeneous mass. The moist mass is passed through a screen with a mesh size of 1.6 mm. The screened granules are dried on racks at about 55°C for 12 hours.

The dried granules are then passed through screens with mesh sizes of 1.2 and 0.8 mm. Highly dispersed silica is mixed with the granules in a suitable mixer for 3 minutes. Then magnesium stearate is added and mixing is continued for another 3 minutes.

The finished mixture is packed into empty size 1 hard gelatine capsule shells using a capsule filling machine.

Example 40

Tablets containing 200 mg of active substance per tablet

Composition:

active substance	200.0 mg
lactose-monohydrate	167.0 mg
microcrystalline cellulose	80.0 mg
hydroxypropyl-methylcellulose, type 2910	10.0 mg
poly-1-vinyl-2-pyrrolidone, insolubly crosslinked	20.0 mg
magnesium stearate	3.0 mg

Preparation:

HPMC is dispersed in hot water. After cooling, the mixture yields a clear solution.

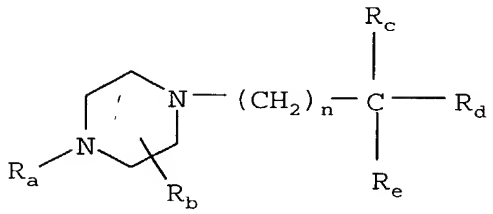
The active substance is premixed in a suitable mixer for 5 minutes with lactose monohydrate and microcrystalline cellulose. The HPMC solution is added and the mixing is continued until a homogeneous moist composition is obtained. The moist composition is passed through a screen with a mesh size of 1.6 mm. The screened granules are dried on racks at about 55°C for 12 hours.

The dried granules are then passed through screens with mesh sizes of 1.2 and 0.8 mm. Poly-1-vinyl-2-pyrrolidone is mixed with the granules in a suitable mixer for 3 minutes. Then magnesium stearate is added and mixing is continued for another 3 minutes.

The finished mixture is compressed in a tablet press to form oblong tablets (16.2 x 7.9 mm).
Weight of a tablet: 480 mg

Patent Claims

1. Substituted piperazine derivatives of general formula



, (I)

wherein

n denotes the number 3, 4 or 5,

R_a denotes a phenyl group substituted by the groups R_1 and R_2, wherein

R_1 denotes a hydrogen, fluorine, chlorine or bromine atom, a C_{1-3}-alkyl group wherein the hydrogen atoms may be wholly or partially replaced by fluorine atoms, a hydroxy, C_{1-4}-alkoxy, phenyl-C_{1-3}-alkoxy, carboxy, C_{1-3}-alkoxycarbonyl, aminocarbonyl, C_{1-3}-alkylaminocarbonyl, N,N-di-(C_{1-3}-alkyl)-aminocarbonyl, nitro, amino, C_{1-3}-alkylamino, di-(C_{1-3}-alkyl)-amino, phenyl-C_{1-3}-alkyl-amino, N-(C_{1-3}-alkyl)-phenyl-C_{1-3}-alkylamino, C_{1-3}-alkyl-carbonyl-amino, N-(C_{1-3}-alkyl)-C_{1-3}-alkylcarbonylamino, C_{1-3}-alkyl-sulphonylamino or N-(C_{1-3}-alkyl)-C_{1-3}-alkyl-sulphonylamino group and

R_2 denotes a hydrogen, fluorine, chlorine or bromine atom, a C_{1-3}-alkyl group or

R_1 and R_2 together denote a methylenedioxy group,

a heteroaryl group,

a monocyclic heteroaryl or phenyl group each of which is substituted by a phenyl or monocyclic heteroaryl group, while the abovementioned phenyl moieties may each be substituted by a fluorine, chlorine or bromine atom and the abovementioned phenyl moieties and heteroaryl groups may each be substituted by a C_{1-3}-alkyl group wherein the hydrogen atoms may be wholly or partially replaced by fluorine atoms, by a hydroxy, C_{1-3}-alkoxy, carboxy, C_{1-3}-alkoxycarbonyl, aminocarbonyl, C_{1-3}-alkylaminocarbonyl or N,N-di-(C_{1-3}-alkyl)-aminocarbonyl group,

R_b denotes a hydrogen atom or a C_{1-3}-alkyl group,

R_c denotes a hydrogen atom,

a C_{1-10}-alkyl, C_{3-7}-cycloalkyl or C_{3-7}-cycloalkyl-C_{1-3}-alkyl group wherein the hydrogen atoms in each case may be wholly or partially replaced by fluorine atoms,

a phenyl, naphthyl or heteroaryl group optionally substituted by a fluorine, chlorine or bromine atoms, by a C_{1-3}-alkyl group wherein the hydrogen atoms may be wholly or partially replaced by fluorine atoms, by a hydroxy, C_{1-3}-alkoxy, carboxy, C_{1-3}-alkoxycarbonyl, aminocarbonyl, C_{1-3}-alkylaminocarbonyl or N,N-di-(C_{1-3}-alkyl)-aminocarbonyl group, by a 3- to 7-membered cycloalkyleneimino group, while the methylene group in position 4 of a 6- or 7-membered cycloalkyleneimino group may additionally be replaced by an oxygen or sulphur atom, by a sulphinyl, sulphonyl, imino or N-(C_{1-3}-alkyl)-imino group, by a nitro, amino, C_{1-3}-alkylamino, di-(C_{1-3}-alkyl)-amino, C_{1-3}-alkylcarbonylamino, N-(C_{1-3}-alkyl)-C_{1-3}-alkylcarbonylamino, C_{1-3}-alkylsulphonylamino or N-(C_{1-3}-alkyl)-C_{1-3}-alkylsulphonylamino group,

R_d denotes a phenyl, naphthyl or heteroaryl group optionally substituted by a fluorine, chlorine or bromine atom, by a C_{1-3}-alkyl group wherein the hydrogen atoms may be wholly or partially replaced by fluorine atoms, by a hydroxy, C_{1-3}-alkoxy, carboxy, C_{1-3}-alkoxycarbonyl, aminocarbonyl, C_{1-3}-alkylaminocarbonyl or N,N-di-(C_{1-3}-alkyl)-aminocarbonyl group, by a 3- to 7-membered cycloalkyleneimino group, while the methylene group in the 4 position of a 6- or 7-membered cycloalkyleneimino group may additionally be replaced by an oxygen or sulphur atom, by a sulphinyl, sulphonyl, imino or N-(C_{1-3}-alkyl)-imino group, by a nitro, amino, C_{1-3}-alkylamino, di-(C_{1-3}-alkyl)-amino, C_{1-3}-alkylcarbonylamino, N-(C_{1-3}-alkyl)-C_{1-3}-alkylcarbonylamino, C_{1-3}-alkylsulphonylamino or N-(C_{1-3}-alkyl)-C_{1-3}-alkylsulphonylamino group, and

R_e denotes a carboxy group, a C_{1-6}-alkoxycarbonyl or C_{3-7}-cycloalkoxycarbonyl group, wherein the carbon atom of the alkoxycarbonyl group linked to the oxygen atom is a primary or secondary carbon atom and wherein the alkyl or cycloalkyl moiety of both groups may be substituted from position 2 in relation to the oxygen atom by a C_{1-3}-alkoxy, amino, C_{1-3}-alkylamino or di-(C_{1-3}-alkyl)-amino group, a phenyl-C_{1-3}-alkoxycarbonyl or heteroaryl-C_{1-3}-alkoxycarbonyl group,

while the abovementioned heteroaryl groups are 6-membered heteroaryl groups containing one, two or three nitrogen atoms, and 5-membered heteroaryl groups, containing an imino group optionally substituted by a C_{1-3}-alkyl group, an oxygen or sulphur atom or an imino group optionally substituted by a C_{1-3}-alkyl group and an oxygen or sulphur atom or one or two nitrogen atoms,

the isomers and the salts thereof.

2. Substituted piperazine derivatives of general formula I according to claim 1, wherein

R_e is defined as in claim 1,

n denotes the number 3, 4 or 5,

R_a denotes a phenyl group which is substituted by the groups R_1 and R_2, while

R_1 denotes a hydrogen, chlorine or bromine atom, a C_{1-3}-alkyl, C_{1-3}-alkoxy, benzyloxy, carboxy, C_{1-3}-alkyloxycarbonyl, nitro, amino, acetamino or methanesulphonylamino group and

R_2 denotes a hydrogen, chlorine or bromine atom or a methyl group or

R_1 and R_2 together denote a methylenedioxy group,

a biphenyl group which may be substituted by a fluorine, chlorine or bromine atom, by a methyl, methoxy or trifluoromethyl group,

a pyridyl, pyrimidyl, pyrazinyl, pyridazinyl or thienyl group optionally substituted by a phenyl group or

a phenyl group substituted by a thienyl, thiazolyl, pyrrolyl, imidazolyl, pyridyl group or benzimidazolyl group,

R_b denotes a hydrogen atom,

R_c denotes a C_{1-3}-alkyl or phenyl group and

R_d denotes a phenyl group optionally substituted by a fluorine or chlorine atom or a methyl or methoxy group,

the isomers and the salts thereof.

3. Substituted piperazine derivatives of general formula I according to claim 1, wherein

R_e is defined as in claim 1 or 2,

n denotes the number 3 or 4,

R_a denotes a phenyl group which is substituted by the groups R_1 and R_2, wherein

R_1 denotes a hydrogen, chlorine or bromine atom, a C_{1-3}-alkyl, C_{1-3}-alkoxy or benzyloxy group and

R_2 denotes a hydrogen, chlorine or bromine atom or a methyl group,

a biphenyl group which may be substituted by a fluorine, chlorine or bromine atom, by a methyl, methoxy or trifluoromethyl group,

a pyridyl, pyrimidyl, pyrazinyl, pyridazinyl or thienyl group optionally substituted by a phenyl group or

a phenyl group substituted by a thienyl, thiazolyl, pyrrolyl, imidazolyl, pyridyl or benzimidazolyl group,

R_b denotes a hydrogen atom,

R_c denotes a C_{1-3}-alkyl group and

R_d denotes a phenyl group optionally substituted by a fluorine atom,

the isomers and the salts thereof.

4. The following substituted piperazine derivatives of general formula I according to claim 1:

(a) methyl 2-ethyl-2-phenyl-5-[4-(4-chloro-phenyl)-piperazin-1-yl]-pentanoate,

(b) methyl 5-(4-biphenyl-4-yl-piperazin-1-yl)-2-ethyl-2-phenyl-pentanoate and

(c) methyl 5-(4-biphenyl-3-yl-piperazin-1-yl)-2-ethyl-2-phenyl-pentanoate,

the isomers and the salts thereof.

5. Physiologically acceptable salts of the compounds according to claims 1 to 4.

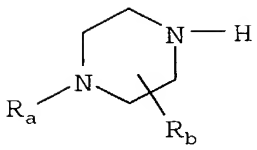
6. Medicaments, containing a compound according to at least one of claims 1 to 4 or a salt according to claim 5 optionally together with one or more inert carriers and/or diluents.

7. Use of a compound according to at least one of claims 1 to 4 or a salt according to claim 5 for the preparation of a medicament having a lowering effect on the plasma levels of atherogenic lipoproteins.

8. Process for preparing a medicament according to claim 6, characterised in that a compound according to at least one of claims 1 to 4 or a salt according to claim 5 is incorporated in one or more inert carriers and/or diluents by a non-chemical method.

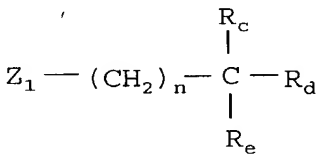
9. Process for preparing the compounds according to claims 1 to 5, characterised in that

a. a compound of general formula



, (II)

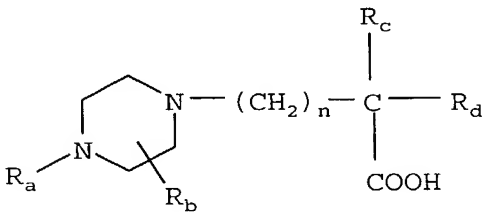
wherein
R_a and R_b are defined as in claims 1 to 4, is reacted with a compound of general formula



, (III)

wherein
n and R_c to R_e are defined as in claims 1 to 4 and
Z_1 denotes a nucleofugic leaving group, or

b. to prepare a compound of general formula I wherein R_e has the meanings mentioned for R_e in claims 1 to 4 with the exception of the carboxy group,
a compound of general formula



, (IV)

wherein
n and R_a to R_d are as defined in claims 1 to 4, or the reactive derivatives thereof, is esterified with an alcohol of general formula

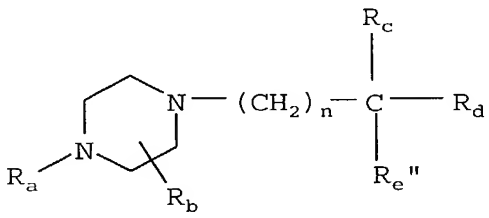
$$H - R_e' \quad , (V)$$

wherein

R_e' denotes a C_{1-6}-alkoxy or C_{3-7}-cycloalkoxy group wherein the alkyl or cycloalkyl moiety may in each case be substituted from the 2 position, relative to the oxygen atom, by a C_{1-3}-alkoxy, amino, C_{1-3}-alkylamino or di-(C_{1-3}-alkyl)-amino group, a phenyl-C_{1-3}-alkoxy or heteroaryl-C_{1-3}-alkoxy group, while the heteroaryl moiety is as hereinbefore defined, or

a tert.butyl ester is prepared by reacting with 2,2-dimethyl-ethene in the presence of an acid or

c. in order to prepare a compound of general formula I wherein R_e denotes a carboxy group, a compound of general formula



, (VI)

wherein
n and R_a to R_d are as defined in claims 1 to 4 and
R_e" denotes a group which can be converted into a carboxy group, is converted into a compound of general formula I wherein R_e denotes a carboxy group, and

subsequently, if desired, a compound of general formula I thus obtained which contains a nitro group is converted by reduction into a corresponding amino compound and/or

a protecting group used during the reactions to protect reactive groups is cleaved and/or

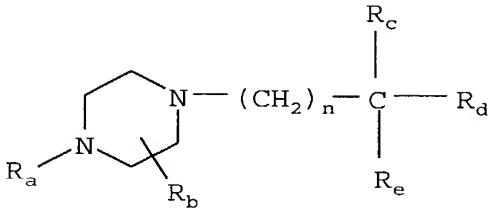
a compound of general formula I thus obtained is resolved into its stereoisomers and/or

a compound of general formula I thus obtained is converted into the salts thereof, particularly for pharmaceutical use

into the physiologically acceptable salts with an inorganic or organic acid or base.

Abstract

The present invention relates to substituted piperazine derivatives of general formula



, (I)

wherein

wherein

R_a to R_e and n are defined as in claim 1, the isomers and salts thereof, particularly the physiologically acceptable salts thereof, which are valuable inhibitors of the microsomal triglyceride-transfer protein (MTP), medicaments containing these compounds and their use, as well as the preparation thereof.

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DECLARATION FOR UTILITY OR DESIGN PATENT APPLICATION (37 CFR 1.63)

☐ Declaration Submitted with Initial Filing OR ☑ Declaration Submitted after Initial Filing (surcharge (37 CFR 1.16 (e)) required)

Attorney Docket Number	5/1269 PCT
First Named Inventor	Thorsten Lehmann-Lintz
COMPLETE IF KNOWN	
Application Number	10 / 049,795
Filing Date	To Be Assigned
Group Art Unit	
Examiner Name	

As a below named inventor, I hereby declare that:

My residence, post office address, and citizenship are as stated below next to my name

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled

SUBSTITUTED PIPERAZINE DERIVATIVES, THE PREPARATION THEREOF AND THEIR USE AS MEDICAMENTS

(Title of the Invention)

the specification of which
☐ is attached hereto
OR
☑ was filed on (MM/DD/YYYY) 08/16/2000 as United States Application Number or PCT International Application Number PCT/EP00/07976 and was amended on (MM/DD/YYYY) _____ (if applicable)

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment specifically referred to above

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.56.

I hereby claim foreign priority benefits under 35 U S.C 119(a)-(d) or 365(b) of any foreign application(s) for patent or inventor's certificate, or 365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or of any PCT international application having a filing date before that of the application on which priority is claimed

Prior Foreign Application Number(s)	Country	Foreign Filing Date (MM/DD/YYYY)	Priority Not Claimed	Certified Copy Attached? YES	NO
DE 199 39 516.0	Germany	08/20/1999	☐	☐	☑
DE199 39 745.7	Germany	08/21/1999	☐	☐	☑
			☐	☐	☐
			☐	☐	☐

☐ Additional foreign application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto:

I hereby claim the benefit under 35 U.S.C 119(e) of any United States provisional application(s) listed below

Application Number(s)	Filing Date (MM/DD/YYYY)

☐ Additional provisional application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto.

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I hereby claim the benefit under 35 U S C 120 of any United States application(s), or 365(c) of any PCT international application designating the United States of America, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U S C 112, I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application

U.S. Parent Application or PCT Parent Number	Parent Filing Date (MM/DD/YYYY)	Parent Patent Number (if applicable)

☐ Additional U S or PCT international application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto.

As a named inventor, I hereby appoint the following registered practitioner(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith: ☐ Customer Number [ ] → *Place Customer Number Bar Code Label here*
OR
☑ Registered practitioner(s) name/registration number listed below

Name	Registration Number	Name	Registration Number
Robert P. Raymond	25,089	Susan K. Pocchiari	45,016
Alan R. Stempel	28,991	Philip I. Datlow	41,482
Mary-Ellen M. Devlin	27,928	Timothy X. Witkowski	40,232
Anthony P. Bottino	41,629	David A. Dow	46,124

☐ Additional registered practitioner(s) named on supplemental Registered Practitioner Information sheet PTO/SB/02C attached hereto.

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Name of Sole or First Inventor: ☐ A petition has been filed for this unsigned inventor

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☑ Additional inventors are being named on the 1 supplemental Additional Inventor(s) sheet(s) PTO/SB/02A attached hereto

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DECLARATION

ADDITIONAL INVENTOR(S)
Supplemental Sheet
Page 1 of 1

Name of Additional Joint Inventor, if any:	☐ A petition has been filed for this unsigned inventor		
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Case No. 5/1269